From the Author

The Croonian Lectures

ON

SOME POINTS CONNECTED WITH SLEEP, SLEEPLESSNESS, AND HYPNOTICS

Delivered before the Royal College of Physicians of London on June 20th, 22nd, 27th, and 29th, 1899

BY

JOHN BUCKLEY BRADBURY, M.D.Cantab.

FELLOW OF THE COLLEGE; DOWNING PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CAMBRIDGE; AND SENIOR PHYSICIAN TO ADDENBROOKE'S HOSPITAL

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LECTURE I.[1]

Mr. President and Gentlemen,—When the late President did me the great honour of asking me to deliver the Croonian Lectures for 1899 I felt some diffidence in accepting the invitation, but on thinking the matter over it occurred to me that some points connected with sleep, sleeplessness, and hypnotics which had engaged my attention might possibly be of sufficient interest to bring before the College. Let me therefore thank the College for the task which was entrusted to me and ask you to consider with me in the first place

The Physiology of Sleep.

Notwithstanding the brilliant and laborious researches of physiologists and neurologists during recent years the phenomenon of sleep is still enveloped in mystery and its study is surrounded with innumerable difficulties. For a long time sleep has been viewed from two standpoints—the physiological and the psychological—and although an attempt to combine the two is sometimes observed they have remained essentially distinct to the present day. It is of necessity so. For notwithstanding the great development of physiological psychology little has yet been done to bridge over the great gulf between the two sciences. It is true that psychologists of the new school are endeavouring to place psychology upon a physiological basis and to correlate psychical processes discoverable by internal perception with physical changes. That every psychical process is accompanied by some physical change seems to be self-evident, but the nature of this change and its connexion with different mental states are problems

[1] Delivered on June 20th, 1899.

difficult to solve. For the present we must be content to regard the relation between the two as one of parallelism. The units of the two sciences are not at present comparable. As Mercier says: "We can no more think of mind and matter in convertible terms than we can imagine a particle of iron to become transformed into a feeling of anger or the revolution of a wheel to become the remembrance of a date of a battle." But as physiology and psychology have joined hands this question of correlation may possibly be solved and the solution is necessary for a true conception of the phenomenon of sleep.

On the basis of recent discoveries in the physiology and more particularly in the histology of the nervous system various theories of the causation of sleep have been advanced, but before we can consider these in detail it is necessary to review our present conception of the central nervous system. The view now current is based upon Waldeyer's idea of a nervous system made up of independent elements—neurons and other cells—intimately interwoven and complexly arranged. Each neuron consists of a cell-body with branching processes (dendrons *or* dendrites, or, according to Sir William Gowers, dendrons *and* dendrites) and an axis-cylinder process (axon *or* axite). The dendrons spring from various parts of the cell-body and divide and subdivide until extremely fine terminal processes (dendrites) are reached, which end, apparently freely, in a homogeneous matrix. In many cases upon the dendrites short lateral offshoots, termed "gemmules" or "thorns," may be seen, and occasionally, especially in the young, nodosities may also be noted. The axon, contrary to former belief, is known to give off branches or collaterals which again subdivide among the dendritic processes of other cells or form a network around their bodies. In no case, however, is direct continuity believed to exist between these. The dendritic processes of one cell are separated from the dendritic processes or collateral branches of another by an intercalated material. Each neuron, in other words, is a unit possessing an independent existence, and as such is comparable to the cells forming other organs of the body. The supposed mode of combination of the various nerve-cells is well seen in this diagram (Fig. 1), taken from Ramón y Cajal's Croonian Lecture before the Royal Society in 1894, and it gives us a better idea of the supposed inter-connexions than can any verbal description. The neurons, as might be expected, vary in the different parts of the brain and cord both in regard to the size, form, and intimate structure of the cell-body and to the form and branching of its processes. But as our immediate purpose is rather with the function than with the size and form of the cell it will be unnecessary to enter in great detail into a consideration of the latter. The anatomical features connected with the function of the cell are alone of interest and latterly these have received considerable attention. As regards the body it is said that the fibrils

of the axon-process can be traced in some cells into the dendrons, and it has been stated that the function of the cell-body in such cases is purely nutritive. Generally in the cell-body a granular formation more or less definitely arranged is observed, the granules around the nucleus being more or less spherical and those at the periphery more elongated. These granules are believed to be connected with the functional activity of the cell; they disappear, for example, from the cells of the cervical ganglion after long-continued electrical stimulation (Vas, Lambert, and Hodge), and the cells of the cerebral cortex, even when affected by ordinary stimuli, show a diminution in their staining power when compared with unstimulated cells (Mann, Lugaro, and Demoor). Changes in the form and volume of the cell have also been described. With moderate activity turgescence of the cell and nucleus and accumulation of chromatin particles occur and after prolonged work shrinking of the protoplasm and irregularities in the contour of the cell and the nucleus are observed. Other changes have been found, but those which I have mentioned are sufficient to indicate that the cell-body is the seat of demonstrable alterations during activity.

All the physiologists who accept Waldeyer's view believe that the transmission of nerve impulses occurs through the intercalated material between the terminal cell-processes, but as some doubt has been thrown on the isolated character of the neurons it will be necessary to inquire into this point further. Our present conception of the nervous system is due almost entirely to investigations with Golgi's silver method, and in this connexion Dr. Alex Hill, in his Presidential Address before the Neurological Society of London in 1896, summarised the objections against the method thus: "1. The deposit is liable to spread beyond the limits of the elements which chiefly attract it. In some cases it stains not the cell or the fibre but the wall of the lymphatic space which surrounds it. 2. The amount and character of the reaction depend upon the texture of the tissue in which it occurs. It is therefore liable to stop short at the edge of a favourable zone, giving an incomplete picture of the elements which it colours. 3. (*a*) It never takes all the elements of any one kind; (*b*) it seldom shows heterologous elements in the same section with sufficient completeness to enable us to trace their connexions; (*c*) it does not stain the whole of the substance which belongs to a cell or a fibre but only part, and this apparently the neuroplasmic not the conducting part" (p. 20). Dr. Hill then proceeds to criticise under these various heads the present accepted views. He throws considerable doubt on the terminal character of axons and their collaterals which form the "basket work" around Purkinje's cells and which Ramón y Cajal describes and believes to be concerned in the transmission of nervous impulses to the cell. But the most important contention of Dr. Hill is the unfairness of concluding from so coarse a method that

the isolation of the nerve elements is complete. The theory just mentioned that nerve-fibres end freely in contiguity with the bodies of nerve-cells, he says, is completely subversive of all existing notions of nerve conduction (p. 25). He then summarises the Gerlachian theory and states that the essential difference between Gerlach's and the modern view (the view of Retzius, Ramón y Cajal, Kölliker, van Gehuchten, and many others) turns upon this: *Is the grey matter a network of continuous strands or is it a felt-work of interlacing but discontinuous fibrils?* As Dr. Hill has taken up the position of counsel for the defendant in this contention and as the subject is one of considerable importance I shall quote him at length. He goes on to say: "The importance of this distinction (that is, the continuity or discontinuity of the nerve fibrils) lies in its physiological application. If grey matter is a network impulses are conducted through continuous circuits. If it is not a network their passage is an *actio in distans*. The substitution of the term 'contact' for 'contiguity' does not help matters physiologically, even if it were justifiable; whereas anatomically it is a gratuitous assumption. It is impossible for a microscopist to distinguish in a preparation stained black between *contact* and *contiguity* of substance. Besides, he has no right to conclude that the position of structures in a hardened and shrunken tissue is the position which they occupy during life." He further goes on to say: "1. The belief in the discontinuity of the elements is based chiefly, although not entirely, upon results obtained with the chrome-silver method. Certainly the figures which this method gives appear discrete; but what is proved by a stain which picks out one cell-system and leaves a number of similar cells uncoloured? In no preparation of the cortex cerebri, for example, could I find fewer than seven pyramids unstained for every one stained; usually the proportion of unstained cells to stained cells is much greater. Supposing for a moment that all these pyramids are united together by their protoplasmic processes, should we recognise it in a preparation in which every stained cell is surrounded by seven cells which are unstained?

"Gerlach's theory, however, did not imply that *homologous elements* are united together. It is more intelligible on the supposition that the large cells (the nutrient cells of long fibres) are not directly connected with one another. Now, when we endeavour to obtain evidence as to the union of heterologous elements we find that the Golgi preparations are almost silent. Hardly ever are two distinct kinds of nerve elements, say branching fibres and nerve-cells, or large nerve-cells and granules, properly and completely stained in the same part of any preparation or even in the same preparation. 2. Even with the chrome-silver method a coarse union between similar cells is shown to be by no means uncommon. These connexions appear to be freaks in development and are of no interest except as

showing that intercellular union is possible. 3. Thorns (*épines*) on the protoplasmic processes of pyramids and cells of Purkinje were first described by Ramón y Cajal, but no attempt has been made to determine their significance. I am inclined to believe that these thorns will eventually give the key to the problem" (p. 28). This is very probable, but before dealing with this question I will quote another paragraph from Hill. He says (p. 32): "I submit that even from the point of view of those who work chiefly with Golgi's method it is a bold assumption that this method shows us the ultimate termination of nerve-fibrils. Speaking for myself I may say that the thought which a good Golgi preparation of the spinal cord suggests is not how complete the picture but how much there must be that one does not see. The amazing delicacy of the last divisions of the collaterals impresses upon one's mind the fact that it is hopeless to try to follow them to their termination since the method is incapable of showing their ultimate subdivisions." I am inclined to agree with Dr. Hill; but in this subject it is so easy to criticise and so difficult to prove. Apart from the observations of Golgi, Waldeyer, Ramón y Cajal, van Gehuchten, and others, my greatest difficulty in accepting the continuous nerve-fibril theory is an *a priori* one. It is that of the cellular constitution of tissues. The various neurons are merely modified cells the processes of which have their birth in the body at some period of embryonic life. According to present views these processes usually grow to a remarkably fine degree and closely approximate, but without uniting. If they unite, what is the cause of their union? It is almost as difficult to accept the idea of the coalescence of these individual dendritic processes as it is to understand the transmission of impulses between isolated cells. Unfortunately it is necessary to settle this question before we can give a satisfactory theory of sleep.

But to return to the thorns or, as they are more frequently called, gemmules. These are short lateral protoplasmic extensions of the final dendritic processes of the neurons. They are most marked on the dendrites of the large pyramidal and Purkinje's cells and they *appear* to end in a rounded knob-like extremity. But do they end thus? Dr. Hill believes that this appearance is purely an artifact and due to the spread of the neuroplasm along the fibrils after death. The thorns, he thinks, indicate an actual union between certain unstained filaments and the protoplasmic processes. In his reseaches on the cerebellum of the skate he saw "in place of thorns on the Purkinje cells long striæ streaming away from the protoplasmic process on either side," and he thinks there is little doubt that the tangential fibres are the axis-cylinder processes of granules. He therefore states that "a direct continuity of structure is established from the granules to the cells of Purkinje" and that "a similar continuity must be looked for in the cortex cerebri and may be expected in the central grey tube" (p. 30). Accepting

this view the transmission of nervous impulses presents no obstacle. Another theory of the function of these gemmules and the transmission of impulses has been put forward by Berkley. He accepts the knob-like terminations of the gemmules as natural, but he cannot accept Ramón y Cajal's theory that nervous forces may discharge themselves from axites to dendrites all along the line. The dendrites he believes, are covered with a thin enveloping sheath through which the gemmules penetrate, and it is only at the tip of the gemmules that naked protoplasm exists. Similarly the fine branches of the axites are covered with "a protective sheath of great tenuity" and only exhibit naked protoplasm at their bulbous terminations. Therefore Berkley believes that it is only between these free terminations that nerve impulses can pass. The mode of branching of the axites varies according as they form ascending fibres (extrinsic) or belong to local cells (intrinsic). The extrinsic break up into a number of filaments, usually at some distance from one another, which re-divide into a small number of others. These course over a short extent of territory and terminate in flattened or globular extremities, the number seldom exceeding six or eight (Fig. 2).

The terminations from the collaterals of the psychical cells show a very different disposition. Winding among the dendrites of the cells and often closely applied to them they seldom show any definite endings until the mid-portion of the layer of small pyramidal cells is reached. There they split up into a number of exceedingly fine branches, which frequently run parallel with the course pursued by the apical and basal dendrites. They eventually give off at frequent intervals exceedingly short collaterals, usually from the side nearest to the dendrites, which terminate in a round or flattened bulb-like extremity similar to those on the branches of the ascending fibres. These are closely applied to the bulbous tip of the gemmules, the appearance often suggesting one of actual contact, the axonal discharges of the stimuli overleaping the infinitesimal distance between the bulb and gemmule (Fig. 1). "The interpretation of the objective existence of the terminal apparatus of the nerve fibres," Berkley says, "cannot be made but in one way—namely, that the impressions conveyed from external sources to central cell and from local cell to local cell are not accomplished by a diffusion of the excitation through the whole cortex, or even at various points along the course of the finer branches of the axons, but at single points perfectly definite in their distribution, and that these points are situated only at the extremities of the nerve-fibre twigs, in the form of an histologically exact formation—the bulbous ending of the nerve-fibre—which in itself constitutes the sole and only means for the carrying over of the cellular forces from axon to dendron and from cell to cell, and is in entire conformity with the conception of Waldeyer of the entity of the neuron, each cell standing as a unit in the nervous formation and only in continuity with others at

definite points." In a still more recent communication Lugaro also states that the transmission of impulses occurs through the extremity of the gemmules. These he believes are capable of expansion and retraction to a slight degree, and upon this function he bases his theory, which I shall presently allude to, of psychical processes. A form of nerve termination in the central nervous system has been described by Aldren Turner and Hunter in the Spring number of *Brain* for 1899; but so far this has not been utilised to explain sleep. After injecting methylene-blue into the circulation during life they found after death a fine lattice-work arrangement over the cells in most parts of the brain. This was most marked over the root of the axis-cylinder process and according to these authors it is the termination of the axis-cylinder of another cell. There is no continuity of tissue and therefore the entity of the neuron is not questioned. Nerve impulses are believed to pass from the network to the cell-body and not from terminal axite to dendrite, or *vice versâ*. The function of the dendritic processes, the authors are inclined to believe, is nutritive—a theory first suggested by Golgi.

After this brief survey of the place of the neuron in nerve-physiology we shall be better able to understand some of the theories which have been put forward to explain sleep. But before dealing with these it will be well to review the facts which it is necessary to explain. Speaking generally, during sleep the whole metabolism of the body is depressed. The respirations are shallower; the aeration of the blood is less active; the pulse is less frequent; the blood-pressure is lower and the temperature tends to fall; the nervous system is so affected that sense stimuli of moderate intensity are not perceived; and consciousness is in abeyance, but reflex effects can still be obtained. These phenomena are not constant during the sleeping state, but vary within fairly wide limits. On this account some of them have been credited with an etiological rôle, and this leads us on to the

Theories of Sleep.

Those advanced up to the present time may be divided into chemical, histological, vaso-motorial, and psychological. These theories are not necessarily antagonistic, as we shall presently see, but their promulgators differ in their mode of explanation and in the prominence which they give to an individual character. Let us first consider the cause of sleep in the abstract.

It is evident that consciousness, whatever this may be, is due to a certain definite condition of the nerve-cells or neurons and any departure from complete consciousness must be due to some change from this state. At the present time it is difficult to come to any other conclusion than that this state and its alterations are of a chemical nature—that consciousness is accompanied by, if not due to, a normal metabolism of the nervous cells, and

unconsciousness or diminished consciousness to a chemical alteration in this metabolism. This so-called normal metabolism is the result not merely of the vital requirements of the cells but of this *plus* the alterations produced by the inflow of stimuli. Diminish the stimuli or make them constant both as to kind and intensity (monotony) and the metabolism may become constant though in changed conditions; a kind of rapid acclimatisation occurs, and with it diminished consciousness. The same effect might be produced by the alteration of metabolism due to the application of a poison. It seems to me that the fundamental phenomena to be determined in dealing with psychical processes are the chemical changes occurring in the cells; molecular vibration and processes of a similar nature which have been speculated upon from time to time are, with our present knowledge, in the realms of the unknown. Even if they can be known it seems more philosophical to determine the gross chemical changes first, although there is not much likelihood of these being actually demonstrated in the near future. Admitting that chemical alterations are the causes or proportional concomitants of states of consciousness we shall be able to trace a connexion in some of the various theories of sleep which have been propounded. Thus, it is very evident that the metabolism of the cerebral cell may be, and probably will be altered by, changed extrinsic conditions—e.g., by the blood-supply—and that it may produce gross physical changes in the cell—e.g., retraction of the protoplasmic processes. The vaso-motorial and histological and in part the chemical theories are—or perhaps it would be better to say may be—thus brought into connexion. But let us examine the theories in detail.

The most fascinating of them all is what Duval has termed the *histological theory* of sleep. This seems to have been propounded in its most rudimentary state by Rabl-Rückhard who suggested that an assumed amœboid motion of the neurons, and especially the dendritic processes, would account for various psychological phenomena. Thus sleep might be explained by a retraction of these processes and consequent inability of nervous impulses to pass from one neuron to another. The same theory was elaborated independently by Lépine and Duval. Lépine thinks this isolation of the individual neurons may be due to some chemical modification of the cellular protoplasm and he also states that the theory explains the extraordinary suddenness with which a state of wakefulness passes into one of sleep. Duval goes so far as to explain the action of medicaments on this theory and he draws comparisons between the action of drugs on the terminal dendritic processes and the effect of curare on motor nerve-endings. This is surely hypothetical. Moreover, he seems to ignore the body of the cell itself; everything is referred to the dendritic terminations. It is most unnecessary to point out that the theory of Rabl-Rückhard, Lépine, and Duval is dependent upon the conception of isolated neurons as

independent units in the composition of the nervous system and that with the disproof of this conception their theory must fall to the ground. Kölliker has strongly criticised this (the amœboid movement) theory. He says that Widersheim's observations on the movements occurring in the nerve cells of the supra-œsophageal ganglion of *leptodora hyalina* are not pertinent to the question, and he rejects the comparison to the action of curare as irrelevant. Widersheim did not observe movement in the processes of the cells; and in the transparent parts of living animals (the larva of batrachians, the head of the amphioxus, &c.), where nerve terminations have been observed, no movement has been perceived. Moreover, he thinks that if amœboid movements occur physical conditions would tend to act in a constant manner and the same mental states under varying conditions would be impossible. Furthermore, he says that "it cannot be doubted that the essential function of the nervous system—i e., psychical processes—is bound up with the nerve cells." In many of his criticisms he seems to me to lay too much stress upon the stability of the axis-cylinder process. The structure of this can hardly be compared with that of the more delicate dendritic processes; and stimuli without influence on the former might powerfully affect the latter. At the termination of his paper he expounds his theory of psychical conditions which although it is necessary to mention is one with which we have long been familiar. The essential factors of mental activity—sensibility, consciousness, will, &c.—he says, are the nerve cells with their neuro-dendritic processes. These are affected by centripetal stimuli and in turn, through their processes, they act centrifugally on other motor, sensory, or psychical elements. Sometimes the pathway is simple, sometimes extremely complex, and in the latter case the degree of mental gymnastics to which the individual has been subjected is of considerable importance as facilitating the transmission along unusual combinations. He is thus an advocate of the view that facility in thought and action is due to diminished resistance in the pathways, but in what way this occurs he does not state.

Ramón y Cajal strengthens Kölliker's objections by the following. 1. The nerve terminations of the cerebellum, the olfactory bulb, the central auditory ganglion, and the optic lobe constantly show the same extension, form, and degree of approximation to the cell bodies, whatever may have been the mode of death of the animal (from hæmorrhage, chloroform, curare, or strychnine, &c.). 2. The nerve terminations of the retina and optic lobule of reptiles and batrachians (the only animals on which he experimented) show the same condition, whether the organ was hardened after continued rest, as after long retention in the dark, or after activity, as when it had been kept several hours in the sun. He therefore believes that the axites and dendrites possess a constant disposition. But in order to explain sleep and other psychical phenomena he brings in another factor. Under different conditions he found the

processes of the neuroglial cells contracted or expanded and he suggests that a function of these cells is to act as an isolating medium between the neurons. During sleep the neuroglial processes are introduced between the nerve ramifications and the cells or their protoplasmic processes, in consequence of which the passage of impulses is prevented or hindered. Apart from the seat of operation, Ramón y Cajal's theory differs from Duval's in that the processes (neuroglial in the case of Ramón y Cajal) are expanded when the brain is at rest and are contracted when in action. The contraction is usually automatic, but may be brought about by the action of the will. I do not, however, propose to follow Ramón y Cajal in his explanation of psychological phenomena on this theory, especially as his observations have not been confirmed by more recent investigators. His theory seems to me to endow the neuroglial cells with more nervous activity than they are capable of and to allot to them a function which, from their position and structure, I venture to think cannot be maintained. Moreover, if we accept the network theory of Boll, Hill, and others, or Berkley's or Lugaro's modification of the usually accepted view, this explanation loses nearly all its significance.

Before leaving the histological theories of sleep I will briefly refer to a view recently advanced by Gotch to explain the conditions of hypnotism. He goes further than Duval in attributing a major influence to the periphery of the neuron, for he believes that the gaps between the terminations of the adjoining dendritic processes are of primary importance in the transmission of nerve impulses. These gaps determine whether an impulse shall pass or not; once it has passed Gotch believes nothing can hinder its further course. The gaps are capable of variation; in fact, he states that "the whole of modern physiology is inexplicable except on the supposition that the gaps are susceptible of alteration. What this alteration is we do not know; the gap consists of living tissue and, like all living structures, is constantly undergoing molecular change." The resistance of the gap varies with different conditions; thus the action of the higher nerve centres increases the resistance; the force of habit or practice diminishes it; constant attention leads to fatigue-changes in the intercalated material, and the forcing of the gaps is then "a concomitant of the mental mood of volitional attention." Although this theory is primarily advanced to explain hypnotic phenomena it is evident that a similar explanation might be advanced to account for sleep. It does not seem quite clear to me whether the resistance is due to a molecular rearrangement of the intercalated material or to an increase of its amount between the dendrites. If the latter, as is suggested in one place, the conditions simulate those advanced by Rabl-Rückhard, Lépine, and Duval. Gotch's theory differs from theirs in attributing a greater influence to the gaps than to the protoplasmic processes. Like its allies it must consequently stand

or fall with the proof or disproof of the neuronic conception of the nervous system. To me it seems to attribute much too active a function to what one has always been taught to regard as a passive structure ; but past teachings must avail little if the present ones are sufficiently convincing: to me they are not.

The most recent theory has been advanced by Lugaro. According to him unconsciousness is not due to a retraction of the terminal dendritic processes but to an expansion. As I have already said, he believes that nerve impulses pass through the gemmules and that the passage is facilitated or inhibited by the closer or remoter relation of these to each other. During ordinary thought but few of these are in contiguity, the others are retracted. The latter are in a potential state—that is, they are capable of being approximated by any suitable stimulus. Lugaro's theory differs from that of Lépine and Duval in that expansion of the gemmules is regarded as the resting phase and contraction as the active one. Thus in sleep the gemmules are believed to be expanded, the paths for impulses are thus enormously increased, and this leads to confusion of thought and loss of consciousness.

In the unsettled state of the views of neurologists on the structure of the nervous system it would be impertinent to criticise these histological theories in detail. Further research alone can settle the present conflicting opinions, and on the result of this depends the probability or possibility of the minute changes which we have considered affording an explanation of psychical phenomena.

The *vaso-motor theory* of sleep is almost as popular as the histological theories which we have considered, and interest in it has recently been awakened by the experiments of Professor Howell of the Johns Hopkins University. It has, however, been a favourite theory for many years. Based upon direct observation of the cerebral cortex by Donders, Durham, Hammond, and others, and on the plethysmographic researches of Mosso, it seemed to possess a firm foundation, but of late this has been rudely shaken. The conditions of experimentation in these researches were not normal and further investigations have shown the necessity of modifying our views on the matter. Thus Dr. Leonard Hill has proved that practically no change occurs in the cranial contents, that the brain at nearly all points is in contact with the cranial wall, and that the amount of cerebro-spinal fluid in the intact cavity is very small and incapable of gravitating to any appreciable extent into the spinal canal. Moreover, he has shown that the cerebro-spinal pressure equals the venous pressure, that it does not rise beyond it, and that the cerebro-spinal fluid does not normally function as a compensating mechanism for alterations in the cranial contents. "The volume of the blood in the brain," he says, "is in all physiological conditions but slightly variable." Therefore, cerebral anæmia, if we regard this as a diminution in the total quantity of blood in the

brain, cannot exist to any extent. It is possible for an arterial anæmia combined with venous congestion to occur, and Dr. Hughlings Jackson's observations on the retinal vessels during sleep would render this not improbable. In view of Dr. Leonard Hill's researches it seems absolutely necessary to recognise the Munro-Kellie doctrine (the incompressibility of the brain and constant volume of the cerebral contents) in dealing with the causal factors of sleep. Cappie on purely theoretical grounds advocated this doctrine and advanced a theory of sleep in harmony with it. The main feature of his view is that the arterial anæmia of the brain is compensated by a filling of the pial vessels and an alteration of the normal pressure on the cerebral surface from an expansive to a compressive force.

Since Dr. Leonard Hill's investigations Professor Howell has advanced a modified form of the vaso-motor theory based upon personal experiments. According to him the anæmia of the cortex is counterbalanced by the dilatation of the vessels at the base of the brain. The causal factor of sleep is a fatigue of the vaso-motor centre and particularly of that part of it supplying the skin area. This Professor Howell deduces from the fact that the volume of the arm increases (that is, the cutaneous blood-vessels dilate) just previously to sleep, and it usually contracts suddenly on awaking. He does not, however, ascribe the production of sleep solely to the fall of blood-pressure, but he regards this as pre-eminent. The etiological factors he gives as follows: 1. A diminution of irritability caused by fatigue of large portions of the cortical area. 2. Voluntary withdrawal of sensory and mental stimuli involved in the preparations for sleep. 3. A diminished blood-supply to the brain owing to a relaxation of tone in the vaso-motor centres and the fall of general arterial pressure thereby produced. Recently Dr. Leonard Hill has criticised Professor Howell's results, or rather his deductions from his results. He finds that the fall of arterial pressure is concomitant with sleep and he adduces confirmatory experiments. Thus he found arterial pressure "as ow when lying in bed in the waking state in the morning as in the sleepy state in the evening"—a result evidently antagonistic to Professor Howell's theory. Moreover, it is not difficult to explain the fall of blood-pressure during sleep, or even previously to sleep, by the posture, the diminution of external stimuli, the extra clothing, &c., which we seek before endeavouring to sleep. The rapid rise of blood-pressure at the moment of awaking Dr. Leonard Hill explains thus: "As the waking state is neared the turgescence of the limbs is lessened owing to the increased tone of the muscles and to the restlessness of the sleeper. Each movement or deep respiration expresses the blood and produces a lesscning in the volume of the arm. This is shown to be so by an examination of Howell's tracings. Since each movement of the body momentarily raises the vena-cava pressure the brain is congested thereby, for the cerebral circulation passively follows every change in vena-cava pressure.

The flushing of the brain is secondary to the external stimuli which provoke the external movements of the body, accelerate the heart, and increase the vaso-motor tone. At the same time these stimuli may awaken the dormant consciousness. Carefully reviewing all the above facts we must, I think, conclude that the anæmia of the brain is caused by rest of the body and the cessation of powerful objective and subjective stimuli. It is the cessation of the latter that produces sleep."

As regards the fall of arterial pressure being *post* or *propter* I agree with Dr. Leonard Hill that it is the former. The vaso-motor theory of sleep is quite inadequate to explain this condition ; nevertheless, vascular phenomena play a part, and an important part, in sleep production. What, then, is the probable condition of the cerebral vessels in sleep ? We have seen that the brain is a closed cavity, that the general arterial pressure falls during sleep, and that the pressure in the intra-cranial veins varies absolutely with that of the intra-thoracic venous pressure ; and it may be further stated that the intra-cerebral blood-vessels have not been shown to possess any vaso-motor innervation. It follows from these and other facts that the arteriole pressure is dependent on the venous pressure and that any diminution in the size of the arterioles must be replaced by increase in size of the veins or other cerebral vessels. Professor Howell believes that the basal vessels dilate, but I am more inclined to agree with Cappie who attributes the greater action to the pial vessels ; probably both sets of vessels are involved. But the condition during sleep, it seems to me, is rather one of comparative blood-stasis than of simple anæmia. In either case a smaller amount of blood passes through the cerebral vessels in a given interval of time and this is in reality the essential factor. And although I cannot regard a fall in blood-pressure as the primary causal factor of sleep, yet the diminished supply of nutriment thus produced must exert a depressing influence on the metabolism of the cerebral cells and aid in sustaining, if not in inducing, sleep. That the fall of arterial pressure is not necessary is shown by the action of many hypnotics, which directly exert no influence in this direction ; but it may also be said that, other things being fairly equal, those hypnotics which depress blood-pressure are more certain sleep-producers than those which do not. Chloral, for example, is more certain than any of its derivatives. Indeed, it seems to me that the evidence of pharmacology in dealing with the various theories of sleep has been too much neglected. Perhaps it has not much to give, but at least it may help in correcting theories framed on other and different lines. The admissibility of pharmacological evidence naturally raises the question as to whether forced sleep from drugs is comparable to natural sleep. Although some hold to the contrary I am inclined to believe that it is. The restorative effect of a properly apportioned dose of a hypnotic in a mild case of insomnia is suggestive. Moreover,

if we accept the idea that sleep is the result of chemical changes in the cerebral cells this conception gains in force, as the introduction of a hypnotic into the organism merely means a change in the environment of the cell with subsequent variation in its activity. To deduce from the narcosis produced by large doses of these drugs that artificially produced and natural sleep are dissimilar is unfair; in this case the stimulus is excessive and the result not comparable. But to return to the theories of sleep.

The various *chemical theories* which have been put forward seem to have been based on insufficient data. With the older theories of Sommer and Pflüger and others I do not intend to deal. But comparatively recently a new chemical theory has been advanced. Errera believes that the leucomaïnes produced by the normal activity of the body play a predominant part. He has based his view mainly on the experiments of Bouchard and his school, who found that during the night convulsant substances were excreted in the urine which were not present during the day. The toxicity of the urine during sleep was found to be much less than that of the urine passed whilst awake. On these experiments Bouchard formulated the theory that during the day the body formed a hypnotic substance which by its accumulation produced sleep and that during sleep a convulsant substance was formed which by inducing muscular movements produced awakening. Both Beck and Herringham have failed to corroborate Bouchard's experiments, but apart from this it is difficult from evidence of this kind to draw conclusions as to the cause of sleep. The urine is a complex body, it varies largely in composition with the kind of food, the amount of exercise, and other physiological and pathological conditions, and this variation is greater with this than with other secretions. It does not seem right to compare the variability of the composition of the urine with the periodic alterations in the temperature and pulse; the limits of the first are much wider. Furthermore, as in the case of blood-pressure, it does not seem to me proved that this altered composition of the urine is not *post* rather than *propter*. I do not mean to imply that metabolic changes have no influence in the production of sleep, but what I do maintain is that sleep has not been proved to be due to any one substance or group of substances present in the urine. The chemical theory from another point of view I shall mention presently.

The fourth class of our division of the theories of sleep is the *psychological*. And here we enter upon difficult ground. We have seen that the physiological and psychological are two separate spheres with independent methods of analysis, that the elements of the two sciences are different, and that the connexion between the two can only be one of parallelism. It may be that we shall never get beyond this stage—that the physical and the psychical even in their simplest forms are not comparable, but from a physiological point of view there seems nothing

improbable in the idea that they may be correlated. Marie de Manacéïne, in a popular book on sleep published two years ago, defines sleep as "the resting time of consciousness," and perhaps from a psychological point of view no better definition could be given; but to me it is a mere statement of a psychological fact, not an explanation. We cannot account for sleep in such an immaterial manner. We may not be able, perhaps, to give any further explanation at present, but the acceptance of such a theory would deprive us of that most valuable aid to research, a working hypothesis. It is not improbable that the new schools of psychological physiology, and especially those which deal with it from the pharmacological side, may help us to a truer conception of the causes of sleep. Wundt and his pupils have already added something in this direction, and it is especially to his pupil Kraepelin that much of our knowledge in this department is due. In a recent paper from his laboratory a new explanation of the action of hypnotics is given. Working on the psychical influence of trional with Kraepelin's methods Hans Haenel found it to diminish the power of calculating and learning by heart, to increase the time in the choice-reaction, to diminish the erroneous reactions, to increase faults and omissions in reading and apprehension, and to diminish the rapidity of writing. He found it, however, to exert no influence on association and muscular work (ergographic curves) nor on the rapidity of repeating things previously learnt. The hypnotic action of the drug is explained, Haenel says, by the depression of apprehension and the increased difficulty in originating coördinate movements. He draws attention to the fact that these, and especially diminished power of apprehension, are present after all hypnotic drugs have been given, and the fact that morphine is not regarded as a hypnotic in small doses is due to the stimulant rather than to the depressing effect which this exerts on psychical processes. This in psychological terms is the condition produced by the action of hypnotics, but as an explanation of sleep it is not sufficient.

If, then, we feel obliged to discard psychological explanations—and with due deference we must do this—we can only return to physical and biological science. As we have said, the fundamental changes must be in the neurons themselves. I am inclined to believe that these are primarily of a chemical character. The differences observed between rest and activity and the changes resulting from the administration of various poisons (Fig. 3), I think, support this view. But these differences are in no sense crucial. Before we could consider them such it would be necessary to know for certain what cells are concerned in the production of mental phenomena and what changes result from the action of hypnotic drugs upon them. The action of poisons on nerve-cells generally is, however, at least suggestive, as it shows that marked changes of a more or less transient character may occur during life. As many

years ago as the year 1876 W. Ludwig, a pupil of Binz, described changes in the nerve-cells of excised and teased cerebral tissue after the application of hypnotics, and came to the conclusion that these, even when well diluted, produce a kind of coagulation of the albumin of the nerve-cells which is not produced by other and closely allied bodies devoid of hypnotic powers. A year later Binz himself described the effect of morphine on isolated nerve-cells. After a time a kind of coagulation-necrosis was produced which did not occur after the application of atropine or cocaine. Strychnine and quinine, however, produced the same effect, so that the action is not limited to hypnotics. More recently the action of poisons has been investigated by means of Nissl's method, and a great number, including many metals, alkaloids, and toxins, have been found to produce distinct changes. Nissl believes that this action is characteristic for the same poison and the same kind of cell, but as yet there is a want of unanimity on this point. That decided morphological changes may be produced by the action of poisons all are agreed, and that these changes may be rapidly produced has been shown by Goldscheider and Flatau in some recent interesting researches. Three minutes after a hypodermic injection of strychnine they found a slight swelling of the nucleolar bodies in some cells, and 12 minutes after an injection, when symptoms (tetanus, &c.) had been produced, changes also in Nissl's corpuscles. The transitory nature of these changes was demonstrated by poisoning an animal with malonic nitrile and antagonising the effect by subsequent injection of sodium thiosulphate. The marked changes produced by the former—the breaking up of Nissl's corpuscles, &c.—were completely antagonised within 70 hours by the latter. The antitoxin of tetanus was also found to possess an inhibiting effect on the changes produced by the toxin. But the morphological changes did not always run parallel with the clinical symptoms. With concentrated solutions of tetanus toxin, for example, the symptoms increased until death occurred, while the changes in the nerve-cells after reaching a certain height slightly receded. Similarly after weak solutions the symptoms increased, while the morphological changes remained stationary or even became effaced. And the same was found to be the case with strychnine and malonic nitrile. The meaning of this we do not know and in the present state of cellular physiology it is hazardous to guess. The function of Nissl's bodies is unknown and their existence under normal conditions has even been doubted. From investigations by Nissl's method, however, there can be no doubt that visible changes, often of a very marked kind, are produced in nerve-cells by the action of poisons, and these we can only regard as of a chemical nature. Changes, too, are produced in the dendritic terminations of the cells, and usually these appear earlier and are more marked than those in the cell-body. But in the dendrites more than in the cell observers differ as

to the exact conditions present. Thus after the administration of morphine Demoor describes nodosities on the dendrites which in extreme cases are reduced to mere moniliform filaments, while Lugaro observed expansion of the gemmules and very slight thickening of the processes. Alterations of the dendrites have been noticed by various observers after hypnotic drugs, and there can be little doubt that transmission of nerve impulses through these must thereby be markedly retarded, if not prevented.

Owing to the differences of opinion of observers regarding the exact condition produced by hypnotic drugs it is impossible to draw a satisfactory conclusion regarding their mode of action or the cause of sleep. I am inclined to believe that hypnotics act chemically upon the neurons, both upon the cell-bodies and their dendrites, and I think histological observations support this view. Retraction of the terminal processes or gemmules, if such occur, I believe to be secondary. But what part is played by the cell-body and what by the terminal processes it is difficult to say. The finer dendrites are probably more exposed to external influences and any modifications in them must affect the transmission of nerve impulses, but the cell-body is the seat of metabolic activity and this, too, must be readily affected by changes in the environment. At the present time there is a tendency to regard the functions of the cell-body as purely nutritive, but although this may be the case with such cells as those of the posterior root ganglia it is probably not the case with the cortical cells of the brain or even with the cells of the spinal cord. But a discussion of this would lead us too far afield and in the end we should have once more to confess our ignorance. Lugaro's view of the action of hypnotics and the cause of sleep I have already noticed. Demoor, as a result of his histological researches, desists from any attempt to formulate a theory of sleep. "Regular and periodic sleep, like the sleep produced by chloroform and morphine, and the inactivity succeeding exaggerated work, finds," he thinks, "its application in part of the facts studied in this work," but the cause of the appearance of sleep he "lays aside, like many others, without a solution," and as regards its intimate nature we with little more knowledge must do likewise.

Turning now to the more immediate object of these lectures I intend to deal with the class of hypnotics in a very general manner. The next two lectures will be devoted purely to pharmacological matters; in the last I propose to deal with the rational treatment of insomnia. The pharmacology will not, however, be solely concerned with the hypnotic influence of the drugs. I intend to take a much broader view and extend my thought to substances which, although they possess no value as medicaments, yet are of considerable pharmacological interest. As the tendency for many years past has been towards a chemical view of pharmacological actions I shall as far as possible take up this line. I propose

first to deal with the hypnotics of the fatty series and afterwards with those obtained from the vegetable kingdom.

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LECTURE II.[1]

GENTLEMEN,—Before dealing with any experimental investigations on the action of hypnotics it is necessary to establish the value of these in therapeutics. In nearly all recent discussions on sleeplessness and its treatment the position of sleep-producing drugs has been assailed, and at the present time, in theory if not in practice, the use of these drugs has sunk to a minimum. This, I think, is to be regretted. Although I do not for one moment countenance a routine treatment of insomnia by drugs I think that these are of considerable value in conditions which I shall mention later. I must add, however, that no class of drugs needs such judicious employment and that resort to them should be had only when other means of treatment are insufficient or contra-indicated.

Having stated my belief in the therapeutic value of hypnotics it next becomes necessary to determine which is the safest and most effective of these. An ideal hypnotic is one which will produce sleep of sufficient duration under all conditions without ill effects or after effects. It is hardly necessary to state that we know of no such remedy at present and it is doubtful if we ever shall. The pharmacological field in this direction at least is limited. The administration of hypnotic drugs produces a condition which is closely allied to, if not identical with, a pathological state. Few if any of these drugs possess a purely selective influence on the cerebral cells, for the cells of other tissues are also affected; but even if they did possess such an influence depression of other organs, circulatory and respiratory, would result from an action on their centres, and the presence of disease might determine a fatal effect of an otherwise non-lethal dose. Moreover, the variability of the individual and the presence of pain and other conditions altogether preclude us from expecting to attain a mathematical adjustment of the induced cerebral depression so as never to overpass the limits of safety. But if we cannot find an absolutely harmless hypnotic at least we can find a comparatively safe one, and it is our duty to determine which is the most reliable and the least toxic for therapeutic purposes. It is intended that

[1] Delivered on June 22nd, 1899.

these lectures should be a contribution in this direction. Much difference of opinion exists as to the best hypnotic and it was thought that a reinvestigation of the matter from an unbiased and strictly comparative point of view might be of service. The classification I intend to follow is mainly a chemical one. In the present lecture I shall deal with synthetic remedies and it will be best to start with the simplest of them—viz., the alcohols.

Although as a hypnotic ethyl alcohol is not largely prescribed by the profession, yet with its homologues it has played an important part in the discovery of newer remedies of this class. The simple constitution of these compounds, the constant presence of what we may regard as a comparatively inactive hydroxyl group, allow us to attribute to the alkyl radicle the effect, and difference in effect, produced by these bodies. Perhaps no other series of organic substances has received so much attention from pharmacologists as this. It has been investigated from every point of view; its general toxic effect and the action on isolated organs and on fermentation processes, &c., have all been determined. As regards the effect on isolated organs, particularly on muscular tissue, an attempt at a numerical relation even has been made. Thus Ringer and Sainsbury from results obtained on the isolated frog's heart state that an increase or diminution of CH_2 in the molecule "is capable of halving or doubling, as the case may be, the activity of the molecule; each CH_2 group may be said in a way to have its physiological equivalent." Other observers, working with other tissues, have not obtained such definite results, although Hemmeter, using the isolated mammalian heart, found that with the exception of ethyl alcohol the toxicity of the series could be expressed by a geometric progression—propyl alcohol being four times more toxic than methyl, butyl twice more toxic than propyl, and amyl twice more toxic than butyl. A similar result was obtained by Dr. J. J. Taylor who worked on simple muscle tissue in my laboratory some years ago. Ethyl alcohol he found slightly less toxic than methyl, whereas the remainder of the series increased in toxicity with increase of molecular weight. The relative influence was, on the whole, greater than Hemmeter's results show, and the variability in effect precluded any deductions of an arithmetical nature. An interesting feature in these tracings is the rapid fall in the height of contraction immediately after the alcoholic saline is applied and the long continuance of contractions of a slight character, notwithstanding the repeated application of the alcoholic solution. It would seem as if a certain amount of tolerance was established unless the phenomenon is due to incapability of the drug to diffuse to the centre of the muscle.

Upon the blood-vessels and blood-pressure the alcohols exert the same general effect as upon striped muscular tissue. The action of ethyl alcohol upon the circulation has been keenly debated, but as a discussion on this point would lead us away from the end we have in view I purposely avoid

it. I shall confine myself to my own experiments on the comparative influence of the alcohols.[2]

When perfused through the vessels of a water tortoise each alcohol causes a transient dilatation followed by contraction; the higher the alcohol in the series the greater is the effect. Methyl and ethyl alcohols are not very active. The following experiment was made in a water tortoise with some of the higher alcohols, the saline running through vessels one and a quarter hours before commencing the experiment. The pressure on the vessels was 18 centimetres of water and the temperature was 16° C. (The numbers represent cubic centimetres running through in each successive five minutes.) Normal saline, 10·0, 9·5, 9·0; 1 in 200 propyl alcohol, 11·0, 18·5, 14·0. Normal saline, 15·0, 10·0, 9·5, 9·0, 8·5, 9·0; 1 in 200 butyl alcohol, 15·0, 20·5, 19·5. Normal saline, 13·5, 8·5, 7·5, 7·0; 1 in 200 propyl alcohol, 7·5, 11·5, 10·5, 9·5. Normal saline, 9·5, 7·5, 6·0, 5·5; 1 in 200 butyl alcohol, 6·0, 12·0, 11·0, 10·5. Normal saline, 7·5, 4·5, 2·5, 2·5; 1 in 200 amyl alcohol, 3·5, 10·5, 13·0, 13·0. Normal saline, 12·0, 8·5, 4·5, 3·0, 3·0.

On blood-pressure, when injected intravenously, methyl and ethyl alcohols exert very little effect. Two cubic centimetres of a 20 per cent. solution are without any influence; larger doses cause a fall varying with the amount given—a distinct rise I have not observed. Propyl produces a slight fall, butyl a more marked one, and amyl alcohol a still greater fall. (Fig. 4.) It has even been suggested that the effect on blood-pressure should be used for determining the presence of higher alcohols in ordinary ethyl alcohol, but considering the similarity in action of these alcohols and the comparatively slight difference in quantitative effect I think the method will be of doubtful utility.

The hypnotic action and toxicity follow the same order as the effect upon simple tissues. As regards toxicity Dujardin-Beaumetz and Audigé[3] obtained the following numbers representing the toxic equivalents measured in grammes per kilogramme body-weight when the alcohols were administered hypodermically to dogs: methyl alcohol, 7·0; ethyl alcohol, 7·75; propyl alcohol, 3·75; butyl alcohol, 1·85; and amyl alcohol, 1·5 to 1·6. Their mode of experimenting has, however, been adversely criticised. The most exact results are those obtained by Joffroy and Serveaux. These observers recognise two kinds of toxicity—a true toxicity and an experimental one. True toxicity they define as the smallest quantity of substance per kilogramme body-weight which will bring about death after a short delay. By experimental toxicity they mean the amount of alcohol required

[2] I speak of these as my own experiments, but I ought to mention that they were performed for me by my late assistant, Mr. C. R. Marshall, now Professor of Materia Medica in the University of St. Andrews, who has rendered me much valuable help in the preparation of these lectures.

[3] Recherches Expérimentales sur la Puissance Toxique des Alcools, 1879; Bulletin Général de Thérapeutique, Sept. 30th, 1884, p. 251.

to cause death when the injection is continued up to the time of death as indicated by stoppage of the respiration. The numbers in this case were found to be—methyl alcohol, 25·25 ; ethyl alcohol, 11·70 ; propyl alcohol, 3·40 ; iso-butyl alcohol, 1·45 ; and amyl alcohol, 0·53. With the exception of the relative innocuousness of methyl alcohol this agrees on the whole with the experiments of previous observers. The toxicity in the case of the higher alcohols is rather greater, but this may be explained by the different method of experimenting. The *true* toxicity differs in many respects from the *experimental* and this is especially the case with methyl alcohol, the toxic equivalent in this case being 9·0 and that of ethyl alcohol being 7·8. According to Joffroy and Serveaux methyl alcohol is not excreted so readily as ethyl alcohol and the great difference in the two kinds of toxicity is thus explained. Quite recently Picard[4] has reinvestigated the question from a different point of view. He used fish, amphibians, and birds. The last he exposed to a definite amount of the vapour of the alcohols ; the first two he treated with triturated solutions of these bodies. The relative numbers he gives are : methyl, $\frac{2}{3}$; ethyl, 1 ; propyl, 2 ; butyl, 3 ; and amyl alcohol, 10. My own numbers as regards the effect on fish—which are, perhaps, the most satisfactory animals to use in order to obtain an accurate relative toxicity—are similar, as may be seen from the following table :—

Alcohol.	Strength.	Death in
Methyl	2·0 per cent.	< 5 – > 20 hours.
Ethyl	2·0 ,,	11½ ,,
Propyl	0·2 ,,	24 ,,
Isopropyl	0·2 ,,	24 ,,
Normal butyl	0·1 ,,	20 ,,
Tertiary butyl	0·1 ,,	22 ,,
Amyl	0·05 ,,	22 ,,

The difference in the numbers given by different observers, especially in regard to the higher alcohols, is probably due to an unequal absorption of these owing to their greater insolubility. But notwithstanding these discrepancies in the actual toxic dose the general fact remains that within limits prescribed by solubility increase of the molecular weight is accompanied by increase of toxicity. As the hydroxyl group remains constant this increase must be ascribed to the alkyl radicle ; and this is further supported by the fact that other compounds (esters, &c.) of these alkyls show the same effect provided that the acid or other radicle has no characteristic action of its own. But the question of importance to us is,

[4] Comptes Rendus, 1897, tome cxxiv., p. 829.

Do we increase the hypnotic power in greater degree than the toxicity by increasing the molecular weight of the alcohol? For it is obvious that in this way alone we can gain any practical advantage which is applicable to therapeutic purposes. With the exception of the greater influence of ethyl over methyl it cannot be said that we do. Certainly not with ordinary amyl alcohol and apparently not with normal propyl and butyl. When we come to the isomers of the primary alcohols the case, however, is different. According to Gibbs and Reichert[5] the toxicity of these when administered hypodermically is as follows: propyl alcohol, 1·6 to 2·5; iso-propyl, 1·3 to 2·0; butyl, 0·3 to 0·6; iso-butyl, 1·3 to 2·0; secondary butyl, 1·0 to 1·5; and tertiary butyl, 1·0 to 1·2. Thus, although iso-propyl alcohol is more toxic than the normal propyl alcohol, iso-butyl, secondary butyl, and tertiary butyl alcohols are much less toxic than normal butyl alcohol. Schneegans and von Mering[6] found the same effect and also showed that secondary alcohols were more hypnotic than primary and tertiary than secondary. Here, then, we have a fact which may be applied to therapeutic purposes. Furthermore, it was found that the component radicles exercised a modifying effect; that, for example, if ethyl replace a methyl radicle in trimethyl carbinol,

a disproportionate increase in the hypnotic action occurs. This substance, which is tertiary amyl alcohol, is known in practice as amylene hydrate. It was introduced by von Mering in 1887 as peculiarly adapted to mental cases, but although it has received a fair trial both in these and other affections it does not appear to have upheld its reputation. According to von Mering it quickly produces sleep both in animals and men without ill effects. It has scarcely any effect on blood-pressure and respiration, except after large doses have been administered, when respiration ceases and the heart stops. But even from an experimental point of view this favourable impression has not been upheld. Vivante[7] found that after small doses both respiration and blood-pressure were depressed; and Jeskow[8] obtained an effect on the heart which he attributed to paralysis of the inhibitory apparatus and simultaneous stimulation of the accelerator mechanism. The most extensive researches on this substance have been carried out by Harnach and Meyer.[9] These observers, like Mering, observed calm sleep in rabbits,

[5] American Chemist, vol. xiii., p. 361.
[6] Zeitschrift für Physiologische Chemie, Band ix.
[7] La Terapia Moderna, iv., 209.
[8] Dissertation, St. Petersburg, 1889.
[9] Zeitschrift für Klinische Medicin, 1894, Band xxiv., p. 374.

but in cats and dogs this was preceded by a state of marked excitement. The blood-pressure was depressed and gradually sank until death occurred. The respirations were increased at first both in number and depth, but later they became weaker, and if a large dose had been given gradually ceased. In men the sphygmograph showed an increase in pulse-tension, the upstroke of the tracing being more slanting and of diminished height, the apex more rounded, and the descent more gradual. The peculiar effects observed were a very marked lowering of temperature (from 4° to 5° C. after moderate doses to rabbits and from 10° to 12° C. after large doses) and an unusual action on striped muscular tissues. The isolated frog's heart showed an enormous temporary increase in contractile power, but this was followed by a sudden fall, irregularity, and death. Given subcutaneously, amylene hydrate produced marked irritation and abscess formation. Other undesirable effects have been described, and it would thus appear, even from purely experimental observations, that amylene hydrate is not a very desirable hypnotic. It is, however, comparatively safe and may be used under certain conditions. Triethyl carbinol, in which the remaining two methyl groups of amylene hydrate have been replaced by ethyl, has been used in 1 per cent. solution in mental cases. The substance only failed to bring about sleep in 4·54 per cent. of cases, but it has a disagreeable taste and produces heaviness of the head and other untoward effects. Of the other alcohols iso-propyl has been recommended as a hypnotic by Friedländer,[10] but it has not, as far as I am aware, been extensively used. In a dose of from one to two cubic centimetres (from 15 to 30 minims) if given in not less than a 12 per cent. solution, it is said to induce sleep in men and to leave no after effects. It produces, however, a burning sensation at the stomach. As it does not appear to possess any advantages over other hypnotics I shall not deal with it further. Tertiary butyl alcohol has been used to produce sleep, but this, too, is of little practical value.

It thus appears that the outcome of investigations on the alcohol series is mainly an indirect one as far as hypnotics are concerned. Within certain limits we have found the value of the alkyl radicles—that ethyl, while differing little in toxicity from methyl, is more powerfully hypnotic and that tertiary alcohols have greater hypnotic properties compared with their toxicity than normal alcohols, iso-alcohols, or secondary alcohols. The importance of this will be seen in the sequel. At this point I might mention the recent work of Albanese on the hydroxy-ethyl methanes. These were investigated to determine the action of the ethyl group in fatty bodies. Four possible compounds exist, but Albanese was only able to obtain dihydroxy-ethyl and trihydroxy-ethyl methanes. The latter was found to be about twice as energetic a hypnotic as the former, but it is also more toxic and less soluble.

[10] Dissertation Berlin, 188

As ethyl possesses marked hypnotic properties we should expect the union of two ethyls by some indifferent radicle or atom to be more markedly hypnotic. This we find to be the case. Ordinary ether, which is composed of two ethyl radicles united by oxygen, $\frac{C_2H_5}{C_2H_5}>O$, is more powerfully depressant to nerve-cells than ethyl alcohol, but it is also more transient in its effect. We have, therefore, evidently to deal with something more than mere chemical constitution and we may perhaps find an explanation in altered physical condition. The physical properties of ether and alcohol differ markedly; ether boils about the temperature of the body, and it is really to its volatility and greater diffusibility that we must attribute its transient action. Were it not for this its inferior solubility in water as compared with alcohol would militate against its more rapid action. This leads me to the question of solubility, which is one of extreme importance and one too frequently overlooked in dealing with the action of drugs. It is obvious, speaking generally, that the more soluble in water a body is the more rapid, transient, and intense will be its effects on the system. A drug slightly soluble in aqueous media will be absorbed but slowly and its action will be delayed, but its effects will be more prolonged. If the substance is quite insoluble only a mechanical effect is obtained. But it is often found that with a diminution in the solubility an increase in toxic action occurs. Thus, in the alcohol series we have considered, amyl is comparatively insoluble, butyl is much more soluble, propyl is still more soluble, while ethyl and methyl alcohols are miscible in all proportions with water. And Richet[11] especially lays stress upon this factor of solubility. He says the more soluble a body is the less toxic it is, and he suggests that this may be due to the inability of the less soluble compound to diffuse evenly through the protoplasm. This question of increased toxicity and diminished solubility refers, of course, more particularly to the substances when compared in solutions of approximately equal strength. If the insolubility of a body is so great as to interfere markedly with its absorption it is obvious that its effect upon the tissue cells of the body must be small. But admitting this we begin to understand why, notwithstanding their difference in molecular weight, methyl and ethyl alcohols are so near each other in toxicity. Richet's explanation, however, is not altogether satisfactory; the question of chemical composition cannot be wholly ignored. In dealing with the comparative actions of any two drugs of any one series we must consider changes both in chemical structure and in physical properties.

Another view of the importance of solubility is that of Meyer and Baum.[12] They point out that von Bibra, Harless,

[11] Dictionnaire de Physiologie, article "Alcools," p. 247.

[12] Archiv für Experimentelle Pathologie und Pharmakologie, May, 1899.

Hermann, Pohl, and others have proved that in animals killed by chloroform and alcohol, &c., there is a disappearance of fat from the tissues containing fat-like bodies such as lethicin in the stroma of the red corpuscles, but especially in the nerve cells of the brain. Meyer and Baum then go on to prove (1) that all bodies nearly chemically indifferent, if they are soluble in fat, have an anæsthetic action, provided they can penetrate to the cells of the brain; and (2) that the relative strength of the narcotic effect of a number of such fat-dissolving bodies is dependent on the one hand on their mechanical affinity with the fatty substances and on the other with the other cell constituents, especially water, consequently the narcotic effect depends on the *coefficient de partage* of the substance when shaken up in equal volumes of oil and water.[13]

Ether is not adapted for a hypnotic, but the allied compounds, methylal and acetal, have been used for this purpose. Methylal or methylene-dimethyl-ether ($CH_2 < \begin{matrix} O.CH_3 \\ O.CH_3 \end{matrix}$) is almost as ill adapted for a hypnotic as ordinary ether. It is a clear liquid, boiling at 42° C. and soluble in three parts of water. From its properties we should expect its action to be transient and this we find to be the case. It was, in fact, introduced into medicine by Richardson as an anæsthetic. Administered to rabbits 1 gramme per kilogramme has scarcely any effect. Slight depression, a slight fall in the number of respirations and in the temperature, and a slight increase in the pulse-rate were all that were noted. Four grammes per kilogramme produced a similar but more marked effect. There was rapid appearance of cerebral depression, the limbs became incoordinate, and soon the animal could be laid on its side, the pulse increased slightly in frequency from 264 to 300 per minute, the number of respirations fell from 78 to 36 per minute and the temperature was lowered 7·9° C. (from 38·6° to 30·7° C.). The vessels of the ear dilated slightly, the pupils first dilated, then contracted, and afterwards dilated again. In two hours the animal commenced to improve and was soon well. The blood-pressure is said to be depressed, but this did not occur when the substance was injected intravenously (Fig. 5). Although comparatively safe, there seems little to recommend it as a hypnotic from an experimental point of view. It has been used subcutaneously in mental cases, but many times, probably because an insufficient dose was given, it was found inactive, and in other cases rapid tolerance was obtained. Circulatory and respiratory depression is said to have occurred, but in such cases this would probably have resulted from any other hypnotic. Methylal seems to be one of the least depressant of hypnotics

[13] Meyer and Baum's view seems to me to be a luminous one—a body but little soluble in water may concentrate in certain cells and tissues to a toxic strength, while a body more soluble in water would not concentrate in this way. Also a certain body may be toxic because it dissolves out something from certain cells.

to the respiratory and circulatory systems, but, as I have said, its transient effect precludes its use.

Acetal (more correctly diethyl acetal) or ethidene-diethyl ether ($CH_3\ CH<^{OC_2H_5}_{OC_2H_5}$) is built up in the same manner as methylal, but it contains instead of the methyl and methylene groups, ethyl and ethidene radicles, and it is also much less soluble. We should therefore expect it to be more active as a hypnotic and more toxic, and this we find it to be. Four grammes per kilogramme given to a rabbit produced rapid narcosis. The pulse fell 24 per minute (from 276 to 252) and afterwards rose again above the normal (to 300). There was distinct dyspnœa, the respirations increasing from 72 to 132 and then falling to 96. The temperature fell 7·2° C. (from 39·5° to 32·3° C.). The blood-vessels of the ear were somewhat dilated and the pupils also were slightly dilated. Recovery commenced in about two hours, but was slower than in the case of methylal. On the blood-pressure acetal again exerted a greater lowering effect than methylal (vide Fig. 5). Thus from an experimental point of view there seems little ground to recommend acetal as a hypnotic and in practice it has been found wanting. It is rather irritant, produces a sensation of burning in the mouth, and leaves an after-smell in the breath. Vomiting sometimes occurs, excitement is not infrequent, and heaviness of the head and giddiness are often present on awaking. In some cases the drug is even inactive. So far as I can see there seems no necessity for retaining it as a therapeutic agent.

Closely allied to the alcohols are their oxidation products, the aldehydes, containing the group $C<^{O}_{H}$ from which is derived the well-known hypnotic paraldehyde. This, as you are aware, is a polymerised product of ordinary aldehyde which itself has a marked cerebral action, being at first excitant and afterwards depressant, and, moreover, powerfully toxic and irritant. Paraldehyde $(C_2H_4O)_3$, consisting of three molecules of aldehyde, differs from its progenitor in being much more stable. It is probably to this chemical stability that its value as a hypnotic is due, although Fröhner[14] has described a reducing effect on the blood. An interesting point in connexion with paraldehyde is the action of metaldehyde $(C_2H_4O)_n$, which, although a polymeride of aldehyde, does not appear to possess hypnotic properties. According to Bókai[15] 1·25 grammes per kilogramme introduced into the stomach of rabbits produces excitement, dyspnœa, tremors, and convulsions, and an increase in the pulse-rate. Paraldehyde itself was introduced into practice by Cervello. Experimentally it produces calm sleep without much depression of the respiratory or circulatory system.

[14] Berliner Klinische Wochenschrift, 1887, p. 685.

[15] Pester Medicinisch-Chirurgische Presse, June 27th, 1886 ; see also Coppola, Annales de Chimie. v., 140.

After two grammes, which were found necessary to produce sufficient anæsthesia, had been given intravenously to a rabbit (1400 grammes) the blood-pressure was found near its normal height, but the respiration soon failed and the blood-pressure consequently fell. Artificial respiration was performed and the heart continued to beat a long time, but the pressure did not rise again. When a solution of paraldehyde was injected into the veins of an animal under chloroform a fall of blood-pressure and an increase in the depth of respirations occurred. After one cubic centimetre of a 10 per cent. solution the effect was very slight; after four cubic centimetres of the same solution it was very marked. A corresponding polymerised product of formaldehyde—paraformaldehyde or tri-oxymethylene—has recently been used as a hypnotic. Considering the greater toxicity of formaldehyde as compared with acetaldehyde we might expect the same of paraformaldehyde as compared with paraldehyde, and this is the case. In man it produces gastric disturbance—vomiting and pain—and it has nothing to recommend it as a hypnotic.

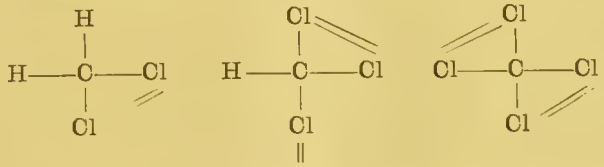
Of the ketones C=O, which are chemical allics of the aldehydes, I shall say very little. None of them are of practical value. Acetone (diethyl-ketone), methyl-nonyl-ketone, and methyl-phenyl-ketone all possess hypnotic powers[16] varying with the size of the molecule and the contained groups. Methyl-phenyl-ketone, under the name "hypnone," was introduced as a hypnotic by Dujardin-Beaumetz but it deservedly fell into disrepute. In many cases it failed to produce sleep at all and even in animals calm and prolonged sleep is not obtained. One gramme per kilogramme injected as an emulsion into the stomach of a rabbit produced paralytic symptoms and sluggish reflexes but little real sleep. The frequency of the pulse fell slightly, that of the respiration moderately, and the temperature markedly (7·5° C.), but the animal recovered. The substance is distinctly irritant and produces a sensation of burning in the mucous membranes with which it comes in contact; and vomiting and other ill-effects are not uncommon. Considering its composition it is rather surprising that it should have been used as a hypnotic at all. Diethyl-ketone has been recommended by Albanese and Barabini as a hypnotic and Nosra[17] has used it in maniacal and hysterical cases, but it is not a substance which is likely to come into general use.

Having determined the general influence of the alkyl radicle the next step in the inquiry is to determine what simple changes in the molecule are capable of modifying hypnotic action. It has been found by numerous experiments that the introduction of a halogen element into an aliphatic molecule almost invariably increases its depressant effect on the brain or initiates this if not previously present. Bromine is the most active in this way, but of the three

[16] Paschkis and Obermayer: Pharmakologische Untersuchung über Ketone und Acetoxime, Leipsic, 1892.

[17] Archivio di Farm. e Terap., iv., 12, 1896.

classes of halogen derivatives the chloro-compounds possess the greatest practical importance. Both bromo-compounds and iodo-compounds have a greater toxicity and they possess other undesirable effects which render their use inadvisable. Until recently it was thought that the hypnotic power of organic chloro-derivatives was dependent on the amount of chlorine they contained. It was found that by introducing chlorine into a simple fatty compound a more marked hypnotic effect was obtained, and that by still further increasing the chlorine the depressant effect on the brain was proportionately increased. The chloro-methane series has often been quoted and has, in fact, served as the stock illustration of this subject. Heymans and de Buck,[18] however, have lately controverted this view. They state that the order of increasing toxicity is not that of the proportionate number of chlorine atoms but is independent of this. By hypodermic administration of the substances dissolved in oil they found the order of toxicity to be as follows: chloroform, 1; methylene dichloride, 2; and carbon tetrachloride, 14. They explain this by assuming a multivalent atomicity for chlorine, thus making chloroform an unsaturated compound. Assuming chlorine to be trivalent the following formulæ would represent the constitution of these bodies :—



Although in many cases—e.g., oxides of chlorine, chlorates, and perchlorates—chlorine must be regarded as multivalent there does not seem much reason for regarding it as such in the compounds under discussion, and even if it were multivalent it would be difficult to understand why tetrachlor-methane was so much less poisonous than dichlor-methane. The question seemed worth re-investigating notwithstanding the careful dosage employed by Heymans and de Buck. It seemed to me that the result obtained by them might be due to difference in absorption, a supposition supported by the fact that carbon tetrachloride is much less soluble in aqueous media than chloroform ; it is also more irritant and possesses greater power of precipitating albumin. In order to obviate as far as possible unequal absorption the toxicity of the two bodies was determined (1) on fish which were allowed to swim in solutions of the same strength ; (2) on frogs exposed to the vapour of the two compounds ; and (3) on rabbits by means of intravenous injection. Fish placed in 1 in 4000 of carbon tetrachloride were more affected than those in a similar strength of chloroform, and the symptoms

[18] Archives de Pharmacodynamie, 1895, tome i., p. 1.

were different. The chloroform produced transient excitement followed by narcosis; the carbon tetrachloride irritation and muscular rigidity, the movements becoming stiff and slow and the tail taking on a permanent curve. In both cases death occurred in about an hour. Methylene dichloride was much less active than either of these substances. A solution of 1 in 2000 produced slight narcosis but not death. Similar effects were obtained from frogs when these animals were placed under a bell-jar with equal amounts of chloroform and carbon tetrachloride. The symptoms first appeared in the animal subjected to chloroform. In this case rapid narcosis and death occurred. In the frog exposed to carbon tetrachloride the narcosis was less deep and muscular rigidity was a prominent symptom. The difference in the time of onset and the severity of the symptoms was undoubtedly due to the difference in the volatility of the two substances and not to any inferior toxicity of the higher chlorinated compound. This latter was more slowly absorbed and the symptoms it produced were more slowly dispelled than was the case with chloroform. When frogs were exposed to the vapours of the drugs and removed as soon as distinct symptoms had developed these symptoms disappeared with rapidity in the case of the frog exposed to chloroform; and only with difficulty in that exposed to carbon tetrachloride. In rabbits the intravenous method was resorted to and considerable difficulty was experienced in finding a suitable medium for the administration of the drugs in this way. Finally, a solution in alcohol, varying in strength up to 55 per cent., was used, and this, containing the chloroform or carbon tetrachloride in solution, was injected into the marginal vein of the ear at the rate of one-half cubic centimetre per minute. In every case much less than the toxic dose of alcohol was employed. Two experiments in which a solution of 1 in 80 of chloroform and carbon tetrachloride respectively in 50 per cent. of alcohol were injected resulted as follows: 2·9 cubic centimetres of the tetrachloride solution quickly produced convulsions and death; 9·0 cubic centimetres of the chloroform solution did not kill for about 12 hours. With weaker solutions larger doses of carbon tetrachloride were given, but in all the experiments the greater toxicity of this drug compared with chloroform was evident. The symptoms, too, were somewhat different; carbon tetrachloride was less narcotic and much more depressant to the heart. Similar results were obtained in rats by intra-peritoneal injection of emulsions of these substances. There seems little doubt, therefore, that carbon tetrachloride possesses a toxicity greater than that of chloroform.

A comparison of these two substances, however, is open to the criticism that the organic radicles in the two cases are not identical. In chloroform we have a hydrogen atom forming with the carbon, a methine group which is not present in the tetrachlor-methane. Moreover, as we have

seen, the symptoms produced by the two compounds are somewhat different. A more logical comparison would be that of carbon tetrachloride and carbon dichloride (C_2Cl_4) or carbon trichloride (C_2Cl_6). The latter is a solid and practically insoluble in water ; the dichloride is a liquid and more comparable in physical properties with carbon tetrachloride. On investigating the toxicity of these bodies on fish the tetrachloride was found to be distinctively the most active. In solutions of 1 in 10,000 of this, minnows died in 40 minutes ; in a similar strength of carbon dichloride they survived more than three hours. It seems, therefore, that as far as the chlor-methanes and allied bodies are concerned, the introduction of chlorine increases the true toxicity, although the apparent toxicity of higher chlorinated bodies, owing to diminished solubility or other property, may be less. But the introduction of chlorine into a fatty compound does not appear to be invariably followed by an increase in toxicity and hypnotic power. A remarkable exception is related by Mayer.[19] He found that the introduction of chlorine into butyric acid did not increase the hypnotic effect—in other words, sodium butyrate was more hypnotic than sodium trichlor-butyrate. The introduction of chlorine into acetic acid, on the other hand, produced the usual effect, sodium trichlor-acetate possessing distinct hypnotic properties, sodium acetate no hypnotic power at all.

In the main I can corroborate Mayer's results. After the intravenous administration of 1 gramme per kilogramme of butyric acid (as the sodium salt) to rabbits, somnolence and paresis were almost immediately produced, but the effect was transient and in two hours the animal was normal. A similar dose of sodium trichlor-butyrate administered in the same way produced a very slight immediate intoxication, but after an hour some depression and somnolence which lasted several hours. It appears, therefore, that the chlorine does possess some action, although this is somewhat tardy. In the case of lactic acid, however, the introduction of chlorine atoms seems to exert no influence whatever and 1 gramme per kilogramme of trichlor-lactic acid neutralised with caustic soda injected into the veins of a rabbit produced very slight depression and thirst, and no further effects followed the administration of 1·5 grammes per kilogramme two and a half hours afterwards. Sodium lactate administered in a similar way produced symptoms quite as marked.

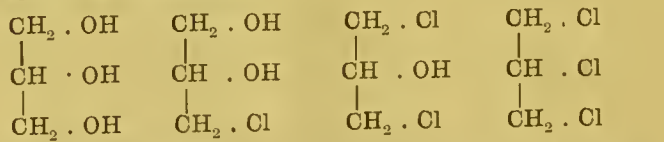
Notwithstanding these exceptions there can be no doubt that in the majority of cases increase in the chlorine atoms of an aliphatic compound leads to an increase in the toxicity and hypnotic effect. This was found to be distinctly the case in the chlorhydrins which were investigated in my laboratory; and a similar influence has been observed in still more complicated compounds. Considering this influ-

[19] Archiv für Experimentelle Pathologie und Pharmakologie, Band xxi., p. 137.

ence of chlorine in organic combination Binz advanced an ingenious theory to account for the action of these bodies. "Certain experimental facts," he says, "appear to show that the haloid soporifics undergo some change in the tissues of the brain, the acid being liberated from the haloid bodies and then paralysing the protoplasm."[20] According to this view the hypnotic effect is a function of the amount of chlorine present, but this is not really the case. Mayer explains the abnormal effect of sodium trichlor-butyrate in this way. This substance, he says, has a greater attraction for the alkaline blood than the acid-reacting tissues, and he believes that a partial decomposition occurs at the time of injection. Kossa[21] thinks that the most important factor is the more or less firm union of the chlorine to the alkyl, and Buchholz[22] states that as regards the chlorhydrins at least the alkyl radicle is not without influence.

But whatever view of the intimate action of the halogen compounds be taken the general law holds good, if we take into account physical properties, that the more chlorine we introduce into an aliphatic molecule the greater is its hypnotic effect. Unfortunately, greater also is its toxic effect; and in the majority of cases the two effects seem to run parallel. This is an important point because it prevents us from utilising the hypnotic power of combined chlorine atoms to the extent we could wish in preparing new compounds. For it is obvious, *cæteris paribus*, that nothing is gained if by increasing the hypnotic power of a drug we at the same time increase its toxic action in an equal degree. What we require in any new remedy is an increased therapeutic efficiency with relatively diminished toxicity.

It is well known that the organic chloro-hypnotics exert a depressing influence on the circulation and it appears that by increasing the number of chlorine atoms we also increase this depressant effect. This subject was investigated by Marshall and Heath[23] in my laboratory. The substances used for this purpose were the glycerine chlorhydrins. These are liquid bodies, more or less soluble in water, the solubility diminishing with each increment of chlorine. For our present purpose they are best regarded as derivatives of glycerine which, as you are aware, is a trihydric alcohol. In mono-chlorhydrin one of the hydroxyls is replaced by chlorine, in di-chlorhydrin two, and in tri-chlorhydrin all the hydroxyls are replaced.



[20] Lectures on Pharmacology: English Translation, New Sydenham Society, 1895, vol. i., p. 199.

[21] Ungarisches Archiv für Medicin, Band xiii., p. 380.

[22] Dissertation, Marburg, 1895.

[23] Journal of Physiology, vol. xxii., p. 38.

When injected into the circulation all the substances produce a fall of blood-pressure : 0·02 cubic centimetre of tri-chlorhydrin produced a greater fall than 0·066 cubic centimetre of di-chlorhydrin, and this a greater effect than 0·2 cubic centimetre of mono-chlorhydrin. A similar influence was obtained on the isolated heart and the blood-vessels and on striped muscular tissue. This depressant effect on the circulation has played an important part in the history of the therapeutics of organic chloro-compounds. Soon after Liebreich introduced chloral hydrate as a hypnotic in 1869 it was recognised that this depressant action would prove deleterious in some conditions. Liebreich himself stated that in heart disease chloral was contra-indicated. To overcome this depressant effect of chloral on the circulation various derivatives have been advocated. Von Mering recommended chloral-formamide (chloralamide) ; Poppi, chloral-urethane ; Nesbitt, chloral-ammonia ; and Richet, chloralose. Chloral-ammonia we may dismiss. It is undoubtedly less toxic than chloral and its influence on the circulation is less marked, but unfortunately it is unstable. After keeping some time it gradually becomes liquid and the smell of chloroform appears. According to my experiments it is the least toxic and depressant of all the chloral derivatives. Langgaard,[24] however, states that doses which produce a light and short sleep produce a marked lowering of blood-pressure and he says that the drug undergoes decomposition even in cold water. In any case its instability prohibits its use.

The effect of chloralamide on the circulation has been keenly debated. It was thought that the combination of an amide radicle—which is believed to possess to some extent the stimulating effect of ammonia upon the respiratory and vaso-motor centres—would diminish the depressant effect of chloral hydrate upon the circulation and respiration, and this was said by von Mering who introduced it to be the case. Similar statements were made by Kny, Reichmann, and Halász. Kny[25] said that the heart was only affected slightly and the blood-pressure was not reduced below that obtained in normal sleep, and Reichmann[26] and Halász[27] saw no injurious action on blood-pressure. Langgaard,[28] on the contrary, obtained a marked action—a slowing of the respiration and diminution of the vessel tone—even with slight hypnosis. He acknowledges a more gradual fall of blood-pressure with chloralamide than with chloral but thinks it is advisable to be careful in its administration in heart disease. Von Mering and von Zuntz[29] controverted Langgaard's statements. They say they have obtained complete anæsthesia without fall of

[24] Therapeutische Monatshefte, 1889, p. 515.
[25] Ibid., 1889, p. 345.
[26] Deutsche Medicinische Wochenschrift, 1889, p. 31.
[27] Wiener Medicinische Wochenschrift, 1889, pp. 38–39.
[28] Therapeutische Monatshefte, 1899.
[29] Ibid., 1889, p. 565.

blood-pressure. Liebreich[30] believes that its action is dependent upon the chloral it contains and that the formamide is an indifferent component. According to Bosc[31] it is "a bad chloral which we ought not to employ therapeutically."

Considering these divergent views it seemed worth while to make a few more investigations with it, particularly upon the circulation. It will be remembered that under the influence of alkalies chloralamide breaks up into chloral and formamide (which becomes ammonium formate) and that this change is supposed to take place in the blood and by some even in the intestines. In my experiments, having regard to Liebreich's view, the doses have been calculated as anhydrous chloral. Thus 1·3 gramme of chloralamide equal 1·12 gramme of chloral hydrate, which contains 1 gramme of anhydrous chloral, and these proportions have been used throughout. Numerous experiments have been made but only types of these will be given. One of the most important is a perfusion experiment through the vessels of a sheep's kidney; here dilute solutions could be used as nearly as possible under normal conditions. Complete solution and therefore equal dosage was insured and the chloralamide-poisoned blood was exposed for some time to a temperature slightly above that of the body. Under these conditions chloralamide was not found to be so active as chloral hydrate and its effect was more slowly manifested. In the following experiment the temperature of the ovens (39° C.) and the perfusion pressure (70 mm. Hg) were kept constant. (The numbers represent cubic centimetres flowing out of the renal vein per minute.) Normal blood, 4½, 4, 3½, 3; 1 in 500 chloral (as formamide), 3, 3½, 6½, 8½, 10. Normal blood, 12, 10½, 7½, 6, 6, 6; 1 in 500 chloral (as hydrate), 5½, 8, 13, 20. Normal blood, 18½, 11½, 7½, 5½, 4½; 1 in 500 chloral (as formamide), 4½, 5, 7, 9½, 11, 12½. Normal blood, 12½, 8½, 6½, 5½, 4½, 4; 1 in 500 chloral (as hydrate), 4, 7, 11, 15½, 19. Normal blood, 17½, 10½, 7, 5, 4.

Experiments on the hind legs of a rabbit with a solution of gum and salt—i.e., with no alkali, so that there could be no decomposition—gave a similar result. In cold-blooded animals (water tortoises) the action on the vessels was not so constant. Generally the effect was similar to that on warm-blooded animals, but occasionally the dilating effect of chloralamide was as marked as that of chloral hydrate or even slightly greater.

On the blood-pressure when injected intravenously chloralamide and chloral hydrate exert the same effect if administered in doses containing the same amount of anhydrous chloral. Thus in Fig. 6, which represents the blood-pressure tracing of a dog, 0·2 gramme chloral injected into the femoral vein produced almost the same fall

[30] Ibid., 1889, p. 568.
[31] Journal des Sociétés Scientifiques, 1890, pp. 27-29.

of pressure whether given as chloralamide or as chloral hydrate. In the case of chloralamide, however, there seems to be a better return to the original height of the blood-pressure, due, it would appear, to more forcible cardiac contractions. Larger doses—0·9 gramme chloral (Fig. 7)—produced similar effects. In the case of chloralamide the medium pressure was reduced from 100 millimetres to 58 millimetres Hg, and it returned again to 98 millimetres Hg. With chloral hydrate the medium pressure fell from 98 millimetres to 56 millimetres and the return reached 97 millimetres Hg. But the fall of pressure in these cases is due in part to a heart effect and if this is avoided as far as possible by slower injection of the drug the greater influence of chloral hydrate on blood-pressure is distinctly brought out. To this I shall return in a moment. On the blood-pressure of the rabbit intravenous injection of the two drugs produced the same effect as in the dog. This is shown in Fig. 8.

But in order to compare the influence of the two drugs upon the circulation under more normal conditions the drug itself was used as the anæsthetic: that is, chloral or chloralamide was injected into the stomach or veins, and as soon as the animal was sufficiently "under" for operative purposes the carotid artery was connected with the manometer and the blood-pressure measured. When injected into the stomach the difference in solubility, and as a result the difference in absorption, of the two drugs leads to a variable quantity of each substance in the blood; but as the point we wish to determine is the arterial pressure when sleep is sufficiently deep to permit operation this is not of great moment. These points are brought out in the tracings. Fig. 9A represents the tracing from a rabbit to which one gramme per kilogramme of chloral as hydrate was given by means of the stomach tube. In 15 minutes the animal was well under and the operation was commenced. The first tracing was taken half-an-hour after the drug had been given and, as you will see, the blood-pressure is already very low, about half its usual height, and it gradually falls; but even after more than three hours a distinct pressure is still maintained and the respiration, although shallow, is still automatic. With the same dose of chloral as chloralamide a very different effect was obtained (Fig. 9B). The operation could not be commenced until after an hour had passed and then the animal was not so deeply "under" as was the case with chloral hydrate. The pressure in this case was little below the normal level when the carotid was joined to the manometer, and although it subsequently fell it rose again and was well maintained six and a half hours after the drug had been given. The explanation of so marked a difference is undoubtedly to be found mainly in the much slower absorption of chloralamide as compared with chloral hydrate, but this is not the whole explanation. In order to obtain a result with chloral hydrate more comparable to that of chloralamide another experiment was performed.

In this 0·5 gramme per kilogramme was injected into the stomach of a rabbit, but as this proved insufficient another 0·5 gramme per kilogramme was given half-an-hour later. Immediately the animal was ready for operation the carotid artery was connected with the manometer and the pressure was taken. Although the animal did not seem to be more deeply narcotised than the chloralamide rabbit the blood-pressure was distinctly lower. Furthermore, in this case the respiration soon began to fail and the animal was allowed to die. In order to overcome the variability in absorption intravenous medication was resorted to. The animal was anæsthetised by injecting a certain amount of chloral, as hydrate or formamide, into the marginal vein of the ear. The solutions used were 1 in 30 and the injection was made at the rate of about two cubic centimetres per minute. As soon as the animal was "ready" for the operation this was commenced. In both cases the conditions were kept as nearly identical as possible. The tracings are shown in Figs. 10A and 10B. The pressure in the chloral hydrate tracing, although of a larger rabbit, is seen to be lower than that in the chloralamide one, but the subsequent fall is not proportionately greater. The respiration in the case of the chloral hydrate rabbit is seen to be more markedly influenced than in the chloralamide one and this effect seems to be constant. It bears out the view that first suggested the use of chloralamide as a hypnotic—that the amide radicle would probably act as a respiratory stimulant. In both experiments repeated injections of the drugs had to be given to maintain the anæsthesia and in the tracings a considerable fall of blood-pressure is noticed. In the chloralamide tracing it seems to be as great even as in the chloral hydrate. In that of the latter, however, a corresponding dose of chloralamide was given for comparison and here the effect is seen to be less marked than with the hydrate. We must therefore come to the conclusion that although when injected rapidly into the circulation chloralamide and chloral hydrate produce the same initial fall of blood-pressure, when given by the stomach or in any way in which the circulation is slowly reached the depressing effects of chloralamide on the heart and blood-vessels are less marked than those of chloral hydrate. The respiration also is not influenced to the same extent. The formamide group cannot therefore be inactive; it plays a part in counteracting the depressant action of the molecule quite apart from its influence in diminishing the solubility. From what I have said with regard to the vascular effects and the solubility of chloralamide we shall not be surprised to find that its toxicity is less than that of chloral hydrate. A dose of the latter corresponding to one gramme per kilogramme body-weight of anhydrous chloral is invariably fatal to rabbits within 24 hours, but these animals always recover from a similar dose given as chloralamide.

LECTURE III.[1]

Mr. President and Gentlemen,—The most important of the other derivatives of chloral is chloralose—a substance first prepared by Heffter and introduced into therapeutics by Hanriot and Richet. It is a substance about which there is much that is deeply interesting. Like chloral hydrate it induces sleep, but instead of depressing reflex activity it markedly increases it. Its toxicity is also greater than that of chloral hydrate, and this is perhaps the most interesting point connected with it. Why a combination of chloral with an inert sugar molecule should so greatly increase its toxic action and modify its effects it is difficult to understand. It may be that the combination presents the chloral molecule to the tissues in a more readily assimilable condition, but this we are not certain of. We do know that chloral combines with glucose and the product thus formed is oxidised in the system to urochloralic acid and this on hydrolysis yields glycuronic acid.

It is mainly to Richet and his pupils that we are indebted for our knowledge of the pharmacology of chloralose. They have chiefly experimented upon dogs. In these animals there is marked preliminary excitement followed by sleep, the muscles retain their tone, and there are increased reflexes, especially to sound; the animal takes up peculiar positions which are half cataleptic, and if the table be hit convulsive movements are obtained. Pain is said to be abolished. The respiratory movements become spasmodic and irregular and finally cease, but the heart is scarcely affected and the blood-pressure is said to be raised above the normal. If artificial respiration be maintained the heart will go on beating some time and comparatively large doses have to be given before it is paralysed. A kind of periodic respiration is described as occurring before death, but the significance of this we do not quite know. In the early stage of its action a peculiar psychical blindness is mentioned by Richet as occurring just as when the angular gyrus (*pli courbe*) on both sides of the brain is extirpated. He believes that the action of the drug is primarily upon the grey matter of the cerebrum, as he found that after its administration the subjacent white matter was more sensitive to stimuli than the cortex, a condition the reverse of the normal. In man the drug is said to produce refreshing sleep without ill effects. The heart and alimentary system

[1] Delivered on June 27th, 1899.

are not affected ; in fact, the blood-pressure is raised and the appetite is stimulated. Muscular twitchings may occur and in some cases even convulsions have been noticed, but Richet thinks that the cases of so-called poisoning are misnamed, and according to him the recorded dangers are in reality advantages, as they show the activity of the medullary and spinal centres. The effect of chloralose in fact, he says, is best expressed by the statement that the brain is asleep and the spinal cord awake, and even excited. The comparative toxicity of chloralose in dogs, cats, and birds per kilogramme body-weight when given by the mouth is as follows :—

—	Dogs.	Cats.	Birds.
Minimum active dose	0·15 gramme	0·005 gramme	0·01 gramme
Hypnotic dose ...	0·25 gramme	0·02 gramme	0·015 gramme
Lethal dose	0·6 gramme	0·1 gramme	0·05 gramme

It will be noticed that cats are extremely sensitive to this drug, but they are also sensitive to chloral and chloroform. My experiments have been made chiefly on rabbits. They react readily to the synthetic hypnotics, the sleep is not preceded by any excitement, they can be kept more under observation, and altogether they are better adapted for comparative investigations than are dogs or cats. In rabbits the same symptoms are seen as in dogs, with the exception of the preliminary excitement—i.e., cerebral depression follows in about half an hour, the animal on attempting to move rolls from side to side, and subsequently sleep occurs. But even then the reflexes are increased, the corneal reflex is distinct, and there may be nystagmus. Pain, however, is not abolished, as heavy pressure on the feet will produce marked reflexes where moderate pressure has no effect. The respiration is slowed and to a less degree the heart-beat also. The temperature falls from the first. A dose of one gramme per kilogramme kills in two and a half hours. Similar effects are produced in guinea-pigs and in rats.

An interesting point in connexion with chloralose, as with all chloral derivatives, is its effect on the circulation. According to Richet, in doses producing complete sleep, this is practically unaffected. If anything the blood-pressure is raised and provided that artificial respiration is maintained it is only after very large doses of the drug have been given that paralysis ensues. In the tracing I show you, however, chloralose distinctly lowered the blood-pressure (Fig. 11). It was taken from a dog to which small doses of chloral in various forms had previously been given (Fig. 7) and it shows the effect of an injection of 16 cubic centimetres of 1·25 per cent. in 20 per cent. of alcohol into the

femoral vein. The blood-pressure is markedly lowered, the heart-beats are slowed, and respiration has ceased. The diminished frequency of the heart-beats in part accounts for the lowness of the pressure. The effect is even greater than a similar dose of chloral hydrate or chloralamide (vide Fig. 7 which shows the effect of these on the same dog subsequently), and that the influence is not due to the alcohol is shown in the succeeding tracing (Fig. 11) which was obtained by injecting the same amount of alcohol without chloralose under exactly similar conditions. When smaller doses were used the effect was less marked, but it still remained greater than with chloral hydrate—at least, when the doses administered were calculated as anhydrous chloral. This is, perhaps, unfair to the chloralose, as, owing to its greater molecular weight, twice as much of it must be administered as of chloral hydrate for the same amount of anhydrous chloral. But the effect is of interest as showing the influence of the chloral component. In a dog weighing 14,400 grammes the injection of five cubic centimetres of 1 per cent. of chloral (as chloralose) in 20 per cent. of alcohol produced slight increase in the respiratory movements, slight dilatation of the vessels, and increased cardiac action. The blood-pressure fell very little, owing probably to the compensating increase in the force of the heart-beat. The same dose of chloral as hydrate produced no action whatever. When double the above doses were used the difference in effect of the two substances was still better shown, the excursion of the stilet after the chloralose solution increasing to a marked degree; after the chloral hydrate solution scarcely at all. The mean blood-pressure after the injection of the chloralose was unaffected; after the chloral hydrate it fell to some extent. When, however, chloralose was used as the anæsthetic the influence on blood-pressure at the onset of anæsthesia was found to be less than with chloral hydrate. This is seen in Fig. 12. To a rabbit weighing 1820 grammes 0·96 gramme of chloralose (0·5 gramme per kilogramme body-weight) suspended in water was injected through a catheter into the stomach. An hour afterwards the animal was laid on its side, but it was not ready for operation for 50 minutes more. When the blood-pressure was first taken (two hours after the drug had been given) it was moderately high, but it rapidly fell. In similar experiments on dogs Richet found no lowering of blood-pressure when the animal was sufficiently anæsthetised to be operated on. The fall in my case may have been due to an excessive dose, but against this view is the fact that the animal was operated on as soon as it was thought to be "ready," the point of departure in all cases, and in reality the time of greatest practical importance. That chloralose depresses the circulation less—and considerably less—than chloral hydrate there can be no doubt, but owing to its greater toxicity I am unwilling to admit its harmlessness in cases of heart disease, in which, as we know, chloral hydrate is strongly contra-indicated.

In the preparation of chloralose another body which has been termed "para-chloralose" is obtained. This is insoluble in water and, according to Richet, it is inactive. Mosso, on the contrary, states that it is very slightly active. I obtained a similar result. To a small rabbit weighing 710 grammes I gave 2·849 grammes of para-chloralose (four grammes per kilogramme) suspended in weak mucilage. Depression and a slight fall in temperature, pulse-rate, and respiration occurred, but no distinct hypnosis. Evidently this substance will be of no practical utility and from this point of view whether it exerts a slight action or not is beside the question.

Besides ordinary chloralose, or gluco-chloralose, other chloraloses exist, and these have recently been studied by Hanriot and Richet.[2] These are galacto-chloralose, arabino-chloralose, xylo-chloralose, and levulo-chloralose. Probably two modifications exist in each case, but they have only been isolated in the arabinose combination. As regards their physiological action arabino-chloralose, para-arabino-chloralose, and levulo-chloralose produce calm sleep without increased reflex activity, and pharmacologically they seem better adapted for therapeutic purposes than gluco-chloralose. They have not, however, been put upon the market and as far as I am aware have not been tried therapeutically. Xylo-chloralose is mainly convulsant and its hypnotic properties are but slightly marked. Galacto-chloralose possesses both hypnotic and convulsant actions, but these are not marked and only appear after comparatively large doses. Of the other chloral compounds which I have investigated meta-chloral is so insoluble as to be almost inactive, and chloral-alcoholate acts in every way like the hydrate and appears to possess no advantages over this compound except a slightly less toxicity, due in all probability to its being less rapidly absorbed. Chloralimide also seems to have no claims to therapeutic consideration. It has been but little investigated. In the case of a small rabbit (960 grammes) which received 2·9 grammes of this substance (three grammes per kilogramme) slight depression was noticed after an hour and subsequently sleepiness, but these symptoms were never very marked. There was a slight fall in the pulse-rate and a distinct fall in the respiratory frequency, but the temperature remained normal. Recovery was very slow. Three days after the experiment the animal was eating very little and distinct tremors were observed on standing. In another case in which a corresponding dose was given to a smaller animal (700 grammes) slight depression but no distinct sleepiness was observed. The animal died in the night. Post mortem the duodenum and upper part of the jejunum were found inflamed and a small amount of serous fluid was found in the peritoneal cavity. Chloral-camphor, a well-known external remedy for neuralgia, probably owing to its slower absorption, is less toxic to rabbits than chloral

[2] Archives de Pharmacodynamie, tome iii., p. 191.

itself, even when the dose is calculated as anhydrous chloral. In man a drachm produced very severe symptoms. It is markedly irritant and possesses no claims to consideration as an internal remedy.

Chloral has also been combined with other bodies—antipyrine, urethane, &c.—and these I shall consider presently. The most recent introduction is a combination of amylene hydrate and chloral to which the name of amylene-chloral has been given. According to Fuchs and Koch[3] it is a good narcotic and possesses no untoward effects. Butyl-chloral hydrate, the old croton chloral, is, as Liebreich stated, an intensified chloral. It corresponds very well in its effects to what we should expect from its chemical relation to ordinary chloral. It is more toxic, more hypnotic, and more depressant to the circulation, but it is much less soluble, and this fact must be remembered in comparing the effects of the two drugs. The bromo-derivatives will not detain us long. Speaking generally, they are less soluble and more toxic than the corresponding chloro-compounds and they are more depressant to the circulation. None of the organic bromo-compounds seem likely to prove useful as hypnotics. Bromal hydrate ($CBr_3CHO.H_2O$), the bromo-compound corresponding to chloral hydrate, is decidedly irritant and rapidly produces toxic symptoms. Thus in a frog while one centigramme of chloral hydrate injected into a lymph sac was not always fatal within 24 hours a corresponding dose of bromal hydrate killed within two hours. Similarly in rabbits 0·5 gramme per kilogramme of chloral hydrate was non-toxic, but the same dose of bromal hydrate killed in less than three hours. The symptoms were marked weakness and heart failure. Post mortem, inflammation of the gastric mucous membrane was found. Bromoform ($CHBr_3$), the correlative of chloroform, is also extremely irritant. It has recently been used as a hypnotic, but it is mostly given in whooping-cough. Considering its toxicity and the ill effects it is liable to produce its use in medicine ought to be abandoned. Ethylene di-bromide ($C_2H_4Br_2$) is also unsuitable as a hypnotic. It is decidedly toxic and deaths are said to have resulted from its use, especially as an anæsthetic. It has been recommended by Donath in epilepsy. Being an organic compound it was thought that it would be easily broken up in the blood and the effect of the bromine more readily obtained. In a rabbit one gramme per kilogramme produced no obvious symptoms beyond slight depression and fall in the respiratory rate and temperature, but the animal died during the night. Bromaloses corresponding to chloraloses have been prepared, but they do not appear to have been investigated pharmacologically. They will probably prove of no therapeutic value. Bromalin (the ethyl ammonium bromide of hexamethyleneamine, $C_6H_{12}N_4C_2H_5Br$) has been employed as a hypnotic and a remedy for epilepsy. It contains comparatively little bromine and consequently is

[3] Münchener Medicinische Wochenschrift, 1898, p. 37.

not very toxic. Four grammes per kilogramme produced in rabbits depression and slight sleepiness of a transient character.

In some cases the analgesics seem to act as hypnotics and an attempt has been made to increase this action by introducing bromine. Bromo-phenacetin ($C_6H_4Br.(OC_2H_5)NH\ COCH_3$) is a case in point. This substance is not, however, very active. Three grammes per kilogramme administered by the stomach tube to rabbits only produced slight depression, fall in the pulse, respiratory rate and temperature. A similar bromo-derivative of antipyrine exists, but this appears to be less efficient as a hypnotic than the phenacetin compound.

Urethanes.

Somewhat more complicated in their molecule than the simple haloid hypnotics are the urethanes—$CO < \frac{NH_2}{O.R}$ —one of which, ethyl urethane (ordinarily called "urethane") was introduced into therapeutics by Schmiedeberg in 1885. Schmiedeberg appears to have been led to its investigation by purely theoretical reasoning, for he says,[4] "it appears *à priori* probable that in them the hydrocarbon group of the fatty series retains the original character of its action, that further the group CO, as the radicle of carbonic acid, by the manner of its combination, will play no important part, and the group NH_2 as far as it possesses any influence must act in the same way as in the ammonia bases and affect the medullary centres." It was therefore only necessary to obtain an unirritating ester of carbamic acid $CO < \frac{NH_2}{OH}$ and this was found in the methyl and ethyl compounds. The propyl ester was not very soluble and the higher esters were almost insoluble in water. Schmiedeberg found ethyl urethane to be a decided hypnotic and in doses which produced sleep it had no depressing influence on the respiration or circulation, the blood-pressure was not lower than normal, and respiration appeared to be stimulated. This is due to the presence of the amide (NH_2) group.

Urethane possesses a slightly irritant effect and after large doses vomiting is induced in dogs. Generally, however, it produces calm sleep without ill-effects or after effects. Its action appears to be more certain in rabbits than in cats or dogs and, I may add, even than in men. With regard to its action upon blood-pressure I showed a tracing of its harmless effect when given by the stomach in my Bradshaw Lecture of 1895. I now add one showing its action when administered intravenously (Fig. 13). In this case it was found that the large dose of 3·5 grammes had to be injected into the veins of a rabbit (1660 grammes) before the

[4] Archiv für Experimentelle Pathologie und Pharmacologie, 1886, Band xx., p. 206.

animal was sufficiently under for operation, yet the blood-pressure was not less than its normal height and was maintained. Subsequently on injecting five cubic centimetres more of a 20 per cent. solution the blood-pressure fell rapidly, but no further fall followed this initial one. The respiration appeared to be scarcely influenced until late in the experiment. Another effect of urethane is a diuretic one; this appears to occur both in man and in animals. Of the other urethanes investigated by Schmiedeberg the propyl ester acted qualitatively like the ethyl compound but more powerfully. The iso-butyl and amyl esters were not investigated. They are, however, comparatively insoluble and are not likely to prove of use in practice. If an ethyl group is introduced into the *amide* radicle the compound produced reacts like ethyl-urethane, qualitatively and quantitively. According to Hübner and Stricker[5] methyl-urethane and ethylidene-urethane are without action. They believe that the influence of the amide group on the medullary centres is antagonistic to the hypnotic effect of the alkyl radicles and if the drugs are given in large doses may even annul it. Later Binet[6] has found both methyl- and ethylidene-urethanes active, the latter being the more active of the two. Methyl-urethane was much less active than ethyl-urethane. This author also found that a hydrogen of the amide group could be replaced by acetyl (C_2H_3O) without changing the character of the action, but that the toxicity of the compound thus formed was decidedly dimiuished.

Besides ethyl, I have investigated methyl-, ethylidene-, and phenyl-urethanes. Methyl-urethane, as previous authors found, is very slightly active. The main effect appears to be diuresis. In frogs one centigramme produced very transient listlessness, and two grammes produced only slight depression, a slight fall in the pulse rate and respiration, and a fall of a few tenths of a degree Centigrade of temperature in a rabbit weighing 730 grammes. Ethylidene-urethane, $CH_3.CH(NH.CO_2C_2H_5)_2$, however, produced marked symptoms. 1·8 grammes suspended in mucilage and given to a rabbit weighing 720 grammes were followed by marked weakness, depression, and sleep. The pulse rate rose and the respiratory rate and temperature fell. No improvement occurred and the animal died in the early part of the following morning. Post mortem blood was found in the urine and petechiæ in the bladder, but with the exception of slight congestion of the upper part of the ileum no other gross lesion was seen. Phenyl-urethane ($C_6H_5NH.CO_2C_2H_5$) was also markedly active but the symptoms were more those of general paralysis than of sleep. A condition simulating catalepsy followed by paralysis, unconsciousness, and a marked fall in temperature (10·2° C. in two hours) were the chief symptoms after a dose of two

[5] Deutsche Medicinische Wochenschrift, 1885, No. 45.
[6] Revue Médicale de la Suisse Romande, 1893, pp. 549, 628.

grammes per kilogramme to a rabbit. The phenyl radicle is here the predominant factor, and whatever may subsequently be found with regard to the hypnotic effect of complicated aromatic derivatives, the simple radicles of this series cannot be used for this purpose. Although increased hypnosis may occur after the introduction of such a radicle this is more than counterbalanced by its increased toxicity. Thus, of the urethanes ethyl-urethane is the only one with any claims to therapeutic utility. Its action appears to be mainly dependent upon the ethyl group it contains, and this effect is again brought out in connexion with the sulphones which we shall notice presently. Quite recently Albanese has investigated the action of di-urethane placed at his disposal by Schmiedeberg. This substance ($NH(CO.OC_2H_5)_2$) contains two oxy-ethyl groups (OC_2H_5), and when administered in doses corresponding to its molecular weight is twice as hypnotic as urethane—an additional proof of the value of the ethyl radicle.

As urethane exerts little effect upon the circulation it was thought that a combination of chloral and urethane would maintain the hypnotic action of the former and at the same time diminish its circulatory depressant power. This was said to be the case by Poppi[7], but Langgaard[8] finds it difficult to understand how the vessel-dilating action of a substance can be annulled by combination with another substance possessing no influence on the vaso-motor centre; and he finds that chloral-urethane—or "ural" ($CCl_3.CHOH.NH.CO_2.C_2H_5$) as it is sometimes called—is less certain as a hypnotic than chloral and that it possesses the same action on the vaso-motor system. Its uncertain effect he attributes to its smaller solubility and slower absorption. In the main Langgaard is right, but I think he is wrong in ignoring the urethane molecule altogether. Theoretically, we might deduce the following conclusion. Assuming urethane to be four times less active than chloral the hypnotic effect of the urethane in the molecule as compared with the chloral must be nearly one-seventh $\left(\frac{89}{147{\cdot}5}\times\frac{1}{4}\right)$, that is, chloral-urethane should be one-seventh less depressant to the circulation than chloral. Practically this amount is insignificant and would not be of much value were it not combined with another and more important factor—viz., that of solubility. Chloral-urethane is but slightly soluble in cold water and readily in boiling. In the latter it is said to be broken up into its constituents, but I have only found this to be the case after prolonged heating. If a mixture of the substance and water be boiled solution results, unless an excess of the material has been added, and on cooling re-precipitation occurs. Furthermore, the solubility seems to be fairly constant for the same tem-

[7] Riforma Medica, 1888, No. 81.
[8] Therapeutische Monatshefte, 1889, p. 515.

perature, and if a slight excess of substance is used this does not quickly disappear on boiling, which would be the case if decomposition occurred with anything like rapidity. In therapeutics at least the supposed decomposition of this substance may be ignored. On account of its composition and smaller solubility chloral-urethane is a safer though a less certain hypnotic than chloral. In rabbits doses corresponding to lethal amounts of chloral produce little effect, but larger doses produce a marked action. Thus, to take a typical case, after 3·65 grammes suspended in mucilage had been injected into the stomach of a rabbit (1120 grammes) the animal rapidly became narcotised, the reflexes were almost lost, the pulse rate fell slightly, the respiratory rate markedly, and the temperature 5·4° C. After four hours slight improvement occurred, but even after six hours this was not marked. The next morning the animal was normal. Thus after a dose of chloral urethane corresponding to two grammes per kilogramme of anhydrous chloral—twice the toxic dose—recovery without apparent after effects occurred. During deep narcosis with this drug the blood-pressure is distinctly lowered, but this does not appear to be so marked as after the use of chloral hydrate.

Sulphones.

Probably none of the more recently introduced hypnotics have excited so much interest as the sulphones. Of these three are on the market—sulphonal, trional, and tetronal. Chemically they may be regarded as methane in which all the hydrogens are replaced by alkyl and alkyl-sulphonic radicles. Thus, sulphonal (disulphone-ethyl-dimethyl-methane) is $CH_3 > C < {SO_2C_2H_5 \atop SO_2C_2H_5}$, in which two hydrogens of methane are replaced by two methyls and the two remaining hydrogens by two ethyl-sulphonic groups. In trional one of the two methyls of sulphonal is replaced by ethyl and in tetronal both methyls are so replaced.

$$CH_3 > C < {SO_2.C_2H_5 \atop SO_2.C_2H_5} \qquad C_2H_5 > C < {SO_2.C_2H_5 \atop SO_2.C_2H_5}$$

The introduction of the two last drugs is due to the fact that the hypnotic influence of sulphonal appears to be dependent upon the ethyls it contains. This was determined by Baumann and Kast[9] after investigation of a large number of di-sulphones. These bodies may be divided into three series—(1) $CH_2(SO_2R)_2$—methylene di-sulphones; (2) $CHR'(SO_2R)_2$—methenyl di-sulphones; and (3) $CR'R''(SO_2R)_2$—ketone di-sulphones, where R., R′, and R″ represent monatomic radicles. These substances react very differently in the body; the last (ketone di-sulphones) are almost wholly decomposed and the first (methylene di-sulphones) scarcely at all. Consequently the ketone-

[9] Zeitschrift für physiologische Chemie, Band xiv., p. 52.

di-sulphones possess the greatest physiological action, the methylene di-sulphones being almost inactive. Between the two both in activity and liability to change within the organism stand the methenyl di-sulphones.

Of the di-sulphones which are decomposed in the organism Baumann and Kast have found that only those were active which contained ethyl groups and that the intensity was dependent on the number of these groups present. Thus sulphonal $\frac{CH_3}{CH_3} > C < \frac{SO_2.C_2H_5}{SO_2.C_2H_5}$ and "reversed" sulphonal $\frac{C_2H_5}{C_2H_5} > C < \frac{SO_2.CH_3}{SO_2.CH_3}$ in which the ethyls and methyls of sulphonal have changed places produce the same effect both qualitatively and quantitatively, and the same action is induced by half the dose of tetronal $\frac{C_2H_5}{C_2H_5} > C < \frac{SO_2C_2H_5}{SO_2C_2H_5}$ which contains four ethyl groups.

Di-methylsulphone-di-methyl-methane, on the other hand, although decomposed within the organism, is almost inactive. Furthermore, six grammes of a di-sulphone containing only one ethyl group—e.g., $\frac{C_2H_5}{H} > C < \frac{SO_2CH_3}{SO_2CH_3}$ or $\frac{C_2H_5}{CH_3} > C < \frac{SO_2CH_3}{SO_2CH_3}$—produced almost the same effects with the same duration as three grammes of sulphonal or other di-sulphone with two ethyl groups. From this it seems proved that the ethyl group is the active factor and that it is immaterial whether these groups are united directly to the carbon nucleus or through an intermediary sulphone linking. The sulphone group, in fact, does not, as such, come into consideration.

Baumann and Kast's experiments were made on dogs, but if we experiment on rabbits the order of activity is changed. Trional is the most potent, tetronal the next potent, and sulphonal the least potent. Evidently in certain cases we have some other active factor than change in mere chemical composition, and this, as I have noted in previous connexions, is change in physical properties. Trional has the lowest melting point of the three compounds and it is also the most soluble, and this is more than sufficient to counteract the increased hypnotic influence of an extra ethyl group in the case of tetronal. In dogs and men, owing to the more liquid gastric contents, more rapid absorption and greater susceptibility to hypnotic drugs, this difference in the solubility of the substances is not so apparent. If experiments are made with complete solutions the order of toxicity—sulphonal, trional, tetronal—is well brought out. Thus fish (minnows) die in about 24 hours when placed in sulphonal 1 in 1600, in trional 1 in 4000, or in tetronal 1 in 5000. It is worth while drawing attention to this marked toxicity of sulphones to fish, especially as compared with other hypnotics. Thus 1 in 500 of chloral is not fatal, and 1 in 1000 of urethane produces scarcely any effect. The symptoms also produced by chloral hydrate and the sulphones

are different in their nature; the main symptom of the first is narcosis; that of the second is paralysis. This suggests that sulphones have some other effect than a purely hypnotic one and that they act on other organs of the body than the brain. This is the case. The prolonged administration of any of these compounds leads to serious conditions and that ill effects are not more frequently manifested after the use of single doses must be attributed to the insolubility of the substance.

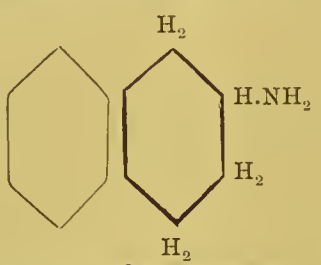
Recently the mode of action and toxic effects of sulphones have been investigated by several observers. Vanderlinden and de Buck have put forward the view that the hypnotic action was due to a diminution in the alkalinity of the blood and a resulting accumulation of CO_2 combined with poverty of O in the nerve cells; but this view has been controverted by Mayser,[10] von Mering,[11] and Giessler.[12] Hoppe-Seyler and Ritter[13] believe that the essential feature of acute poisoning by these drugs is a destruction of red blood corpuscles and that this accounts for the siderosis of the liver, the excessive formation of bile, and the presence of urobilin in the urine. Fatty degeneration and sometimes necrosis occur in the heart, liver, kidneys, stomach, and intestines; and secondary symptoms—e.g., blood stasis in the organs from heart failure—also result. Death in warm-blooded animals is said to occur from broncho-pneumonia (aspiration pneumonia).

Vegetable Hypnotics.

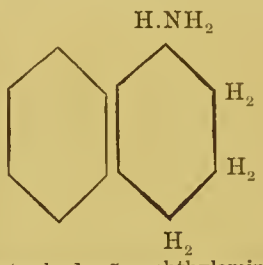
Passing on now to the vegetable hypnotics it is not possible to deal with these on purely chemical lines. The active principles of some of them are unknown and even of those which are known we are imperfectly acquainted with their chemical constitution. Yet before a chemical classification is possible this must be completely determined. We are aware that many of them contain definite groups, and in the case of some we know the parent radicle, but the mode of combination of the various groups in these cases is still uncertain. From a pharmacological point of view this mode of combination is of importance, as drugs possessing the same empiric formula, and even in some cases similar constitutional formulæ, have very different pharmacological actions. Thus, Filehne found that the tetrahydronaphthylamines differed markedly in their action, according to the position of the amide group; alicyclic tetra-hydro-β-naphthylamine being a mydriatic and producing contraction of the vessels of the ear and other effects; the corresponding tetra-hydro-α-naphthalmines having no such action. Cash and Dunstan also found that tri-acetyl-benzoyl-aconine possessed a very different

[10] Deutsche Medicinische Wochenschrift, 1896, p. 185.
[11] Therapeutische Monatshefte, 1896, p. 421.
[12] Dissertation. Halle, 1896.
[13] Münchener Medicinische Wochenschrift, 1897, pp. 355, 391.

effect from that of di-acetyl-aconitine, although aconitine is acetyl-benzoyl-aconine; and numerous other examples might be given. Owing to this uncertainty regarding the composition of the active principles of plants, most of the pharmacological work in connexion with their chemical constitution has been done upon those outlying groups



ac.tetra-hydro-β-naphthylamine.



ac.tetra-hydro-α-naphthylamine.

which we know to be present. Modifications of the original substance, such as by the introduction of simple radicles, have been submitted to pharmacological investigation and have given us interesting results, these being in some cases even of practical value. This will be seen presently.

As opium is by far the most important of the vegetable hypnotics that we possess I shall deal first with this substance. It has now been known for over 2000 years and during the whole of this time it has formed one of the staple ingredients of the materia medica. At one time or other it seems to have been used in every conceivable disease and condition, and although the result has not always been beneficial to the patient the knowledge which has been gained is of inestimable value to us at the present day. We might even go so far as to say that it is of paramount importance; that physiological investigation has added little to our knowledge of the therapeutic uses of opium. It has confirmed the knowledge which we had previously acquired in another and more undesirable way and it has given us a more rational basis for its employment in practice. The beginning of our scientific knowledge of opium only dates from the commencement of this century when Sertürner isolated morphine. This, the first alkaloid to be obtained, was found to possess similar effects to opium and on this account it aroused considerable interest. Pharmaceutical research was stimulated and soon a number of other alkaloids and principles were extracted from plants. Besides morphine other alkaloids were also obtained from opium and in time these were investigated pharmacologically. In this connexion Claude Bernard's name stands out pre-eminently. It was early found that all the alkaloids of opium were not possessed of similar effects. Some, such as morphine, produced cerebral depression; others, such as thebaine, excitement and convulsions. Thus

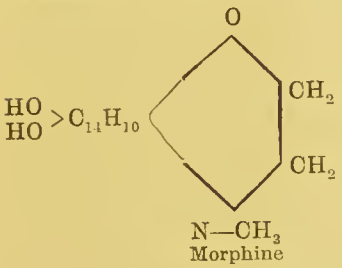
within the same vegetable product were found substances possessing antagonistic actions. But further investigation proved that the two substances were not so antagonistic as was at first thought. Morphine was found to act differently on different animals—in the frog producing mainly convulsions and in some mammals excitement rather than depression. These mammals are said by Guinard, who has recently made an important contribution to this subject, to be the horse, ass, ox, cat, sheep, pig, and goat; the dog, rabbit, guinea-pig, white rat and mouse, on the other hand, are more or less depressed. Even in the same species of animals there is a considerable variation in the action of morphine, and men, who are most susceptible to its depressant effects, are sometimes markedly excited by it.

Comparatively recently Amblard and Grasset have returned to the question of the convulsant action of morphine, and from researches on animals with cut spinal cords have concluded that morphine and thebaine are not diametrically opposite in action and that the effect of morphine on frogs and mammals is not dissimilar. This was previously known, but these authors lay stress on the fact that the excito-motor action of opium is not exclusively dependent on the amount of so-called convulsant substances it contains, but it is also partly due to the morphine present. An amount of opium containing five centigrammes of morphine is more convulsant than the amount of thebaine (about one milligramme) present. But whatever the effects in other animals, to man and the dog morphine is decidedly depressant and differs markedly in its action from thebaine. And according as the other alkaloids of opium approach nearer to one or other of these in action they may be classified. Claude Bernard commencing with the least convulsant obtained the following series: narceine, morphine, codeine, narcotine, papaverine, and thebaine. The order of toxicity he found was: narcotine, morphine, narceine, papaverine, codeine, and thebaine, the last-named being the most powerful. Schröder divides the alkaloids of opium into two groups: the morphine group containing morphine and oxydimorphine; and the codeine group containing papaverine, codeine, narcotine, and thebaine. Hydrocotarnine, laudanosine, and cryptopine also belong to this group, but our knowledge of their actions, Schröder says, is not sufficient to place them. Hans Meyer, in connexion with a research on other papaveracious alkaloids, has modified this classification. He divides them thus: 1. Morphine group, containing morphine, chelidonine, and α-homochelidonine. 2. Codeine group, containing papaverine, codeine, laudanosine, narcotine, hydro-cotarnine, sanguinarine, thebaine, laudanine, and hydrastine. 3. Protopine group, containing protopine, β-homochelidonine, and cryptopine. Not one of these classifications seems to me satisfactory. Claude Bernard's classification has been criticised by many observers, mainly in connexion with the relative positions of morphine and narceine. The latter in men has not been found by the

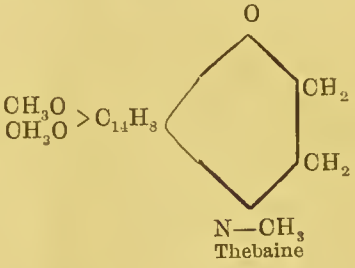
majority of observers to be more narcotic than the former, and in practice it has proved of little value. The position of papaverine in the two classifications also seems to me erroneous. In both it is given as a convulsant and in Bernard's as a marked convulsant. In my experiments the prominent symptom has been depression. In frogs spasmodic incoördinate movements may sometimes be obtained on stimulation for a short time after the administration of a lethal dose, but at no time is any tetanus or marked increased activity present. In rats 0·3 gramme per kilogramme produced muscular weakness, slowing of the pulse and respiration, but no tetanus or distinct narcosis; the symptoms lasted four hours and recovery occurred. Still larger and lethal doses failed to produce increased reflex excitability. In a guinea-pig 0·2 gramme (0·47 gramme per kilogramme) produced prostration and running movements of the limbs which lasted 30 seconds, but these often occur after the administration of alcohol and they cannot be regarded as certainly indicating a convulsant action. The animal died from paralysis of the respiration in 10 minutes. A rabbit to which a similar dose (0·48 gramme per kilogramme) was given also died in 10 minutes, and in this case the heart and respiration ceased together. No sign of narcosis, rigidity, or tetanus occurred. It seems to me that these experiments show that papaverine is not possessed of any convulsant action in any sense of the word. As far as I can see its action is mainly depressant, and as the nerves still retain their irritability after death the effect is apparently due to an action on the central nervous system.

My experiments with the other alkaloids corroborate, on the whole, those of previous observers. Thebaine is almost a pure convulsant and the same may be said of laudanine and laudanosine. Hydro-cotarnine, protopine, and codeine also possess convulsant properties and so does morphine in frogs and many mammals. Protopine produces more clonic convulsions than the other alkaloids, but this does not seem sufficient to justify its being placed in a separate division. Narcotine and cryptopine I have not found markedly convulsant and narceine seems to possess no action whatever in this direction. Von Schröder found it without effect when given per os to a rabbit, and in a kitten to which 0·1 gramme per kilogramme was given by the mouth I obtained no action. Injected intra-peritoneally into a rat 0·5 gramme per kilogramme (1·25 cubic centimetres of 2·5 per cent. solution) only produced slight and transient depression, and in a frog 0·02 gramme produced after some time depression, followed in a few days by death. Previously to death the animal became slightly tetanic when touched. The order of toxicity, according to my experiments, is—narceine, narcotine, morphine, codeine, papaverine, hydrocotarnine, laudanosine, laudanine, protopine, and thebaine. As regards therapeutic utility none of these substances, except those already in use (morphine and codeine), are likely to prove of value in practice.

I have said already that we know comparatively little of the chemical constitution of these bodies, but it will be interesting, and perhaps not unprofitable, to compare for a moment the actions of these alkaloids in the light of our present knowledge of their constitution. And as morphine and thebaine represent the two physiological types of the morphine alkaloids we will take these. Chemically they are closely allied—more closely than we should expect them to be from their physiological effects—morphine being a derivative of tetra-hydro-phenanthrene and thebaine of di-hydro-phenanthrene. Morphine contains two hydroxyl groups—one alcoholic and the other phenolic—and thebaine two methoxyl groups. Thebaine, therefore, differs from morphine in possessing two methyl groups in place of the two hydrogens of the hydroxyl and in containing two hydrogens less in the remaining radicle. This is seen in the following formulæ :—



Morphine



Thebaine

It is open to us to assume that the pharmacological influence of the last-named hydrogens is small, and if we do this we should then turn our attention to the methoxyl groups. We know that methyl when introduced into some alkaloids produces profound changes in the pharmacological action of these, so that *a priori* there is nothing improbable in the view that the difference in action between morphine and thebaine might be due to these methyl radicles. The view is even supported by the fact that codeine, which is morphine with one hydroxyl group replaced by methoxyl, is intermediate in tetanising power and toxic effect between this and thebaine. Laudanine ($C_{17}H_{15}N$ (OH) $(OCH_3)_3$) and laudanosine ($C_{17}H_{15}N$ $(OCH_3)_4$) which are closely allied to thebaine in pharmacological action also contain methoxyl groups, but the position of these is unknown and the comparison does not help us much. It shows us, however, that the tetanic effect does not go on increasing with the number of methoxyls, as laudanine which contains three is less powerful than thebaine containing only two, and laudanosine containing four is still less powerful. Evidently the presence of methyls in other parts of the molecule has a weakening effect on the convulsant action. The other opium alkaloids possessing tetanising effects cannot be compared in this connexion. Protopine is said by Schmidt and Selle not to contain methoxyl groups at all. If a higher alkyl than

methyl be introduced into morphine the convulsant action is said to be still further increased. Thus codethylin, which is morphine in which one of the hydroxyls has been replaced by ethoxyl, is more powerful than codeine (methyl morphine). Von Schröder has even advanced a general law: if a hydrogen of morphine be replaced by an alcoholic radicle ($C_n H_{2n+1}$), as n increases the tetanising and paralysing action of the alkaloid increases: $C_n H_{2n}$ and $C_n H_{2n-1}$ act in the same direction.

But to return to morphine. The general action of this drug is well known to all of you and I have nothing new to add as to its effects. I have already called your attention to the fact that in many animals it produces excitement rather than sleep, and that even in men excitement, sickness, and other untoward effects instead of sleep sometimes follow its use; but in the majority sound sleep is produced. It cannot, however, be employed habitually as a hypnotic, mainly on account of the rapid tolerance which is produced, and also on account of its tendency to induce a habit and produce untoward effects on the system. But whenever pain is present morphine is the hypnotic *par excellence;* to this I shall return in my next lecture. With morphine we have no longer to deal so much with a depressant effect on the circulation, as in the case of chloral and its allies, as with an effect on the respiration. This comes out in nearly every tracing taken with this drug. At first there is often increase in the frequency and depth of the respirations, and sometimes this effect may last a considerable time, but during the sleep produced by the drug the respirations are almost invariably slower and often shallower. Later they may become irregular and rapid or may take on a periodic rhythm simulating that which is known as Cheyne-Stokes' respiration. The irregularity, cessation, and subsequent re-commencement at a slower rate of the respiration is well shown in the annexed figures (Fig. 14 A, B, C) taken from Guinard.[14] It is that of a dog (16 kilogrammes) to which eight centigrammes of morphine hydrochloride were given intravenously M represents the blood-pressure, P the pulse, and R the respiration. The arrow shows the time of commencement of the injection. The respiration rapidly becomes irregular and then ceases; afterwards it re-commences but at a much slower rate. The same effect is usually obtained in other animals. From a rabbit which had been given morphine intravenously until just anæsthetised the tracing shown in Fig. 15 was obtained. It shows a slower respiration than normal. The blood-pressure is also under the normal and this is the usual condition in morphine sleep. According to Guinard the effect of morphine on the circulation varies somewhat according as the animal is narcotised or not by the drug. In animals which are narcotised, such as the dog, the blood-pressure at first rises and then falls below the normal to the extent of

[14] La Morphine et l'Apomorphine, 1898.

about 20 millimetres of mercury. In animals not narcotised there may be a preliminary fall, but the pressure afterwards rises and remains above the normal level until near death. The heart itself Guinard believes is stimulated directly, more especially in those animals which are not narcotised by morphine. Thus in a sheep the tracing of the heart, shown in Fig. 16, was obtained before N. and 10 minutes after A. 25 centigrammes of morphine. After large doses in the dog the heart-beat sooner or later becomes irregular, taking on sometimes a bigeminal character and not unfrequently abortive beats—beats rapidly following a previous one and insufficient to influence the pulse—occur. (Fig. 17.) The irregularity he is inclined to attribute to a central action; as section of the vagus caused it to disappear. This is of importance in connexion with the use of morphine as a hypnotic in advanced heart disease, for although in this condition it is one of the best hypnotics we possess it is by no means free from danger. Guinard's observations point to the cause of this.

Apart from its use in heart and lung disease the other untoward effects of morphine are perhaps of more importance. After its use in any form, more or less depression, headache, anorexia, and constipation result and occasionally even more serious symptoms. Some of these—such as the constipation—can be rectified by medicinal treatment, but it would be difficult, even if it were advisable by such methods, to counteract the ill effects of morphine under all conditions, and consequently attempts have been made to find less dangerous and equally effective substitutes. To two such compounds I intend to draw your attention in the next lecture.

LECTURE IV.[1]

Mr. President and Gentlemen,—I concluded my last lecture by stating that attempts had been made to find less dangerous and equally effective substitutes for morphine. To two such compounds I now wish to draw your attention.

In 1890 Stockman, in conjunction with Dott,[2] published experiments made on some derivatives of morphine. They introduced into the morphine molecule various alkyl and acid radicles and chlorine (substitution products) and also modified it by the addition of methyl chloride (addition product). As we have seen, morphine contains two hydroxyl groups, and the hydrogen of one of these, probably united to an aromatic nucleus, is more easily replaced than the other. When this is replaced by methyl, ethyl, or amyl the morphine action still remains, but the compounds thus produced are more toxic, their narcotic power is less, their tetanising power is greater, and they have a greater effect upon the motor nerves. On the whole their experiments do not seem to give much support to Schröder's law, as they say: "Theoretically, there is possibly a difference in the actions of the three substances, but it must be entirely quantitative, not qualitative, and our methods of investigation were not sufficiently fine to detect it (if it really exists)." Von Mering's recent observations are even more convincing. From clinical observation he found propyl-morphine, isobutyl-morphine, and amyl-morphine distinctly feebler than methyl- and ethyl-morphines. "The majority of the patients," he says, "clamoured for the two last-named substances."[3] When acetyl and benzoyl radicles were introduced and acetyl-morphine, diacetyl-morphine, benzoyl-morphine, and di-benzoyl-morphine thus produced a similar effect was obtained; the narcotising action was less and the tetanising action was greater than in the case of morphine; the heart was also more affected. The narcotic effect, however, is present after small doses (one milligramme—$\frac{1}{2}\frac{1}{0}$th grain—of acetyl morphine in the case of rabbits), but it does not appear to increase with increase of the dose, tetanic symptoms developing instead. "The depressant action of small doses on the cord, and especially on the respiratory centre," Stockman and Dott say, "is very much greater than that of morphine." From this statement we should not expect any of these to be of value as substitutes for morphine. But

1 Delivered on June 29th, 1899.
2 Brit. Med. Jour., vol. ii., 1890.
3 Merck's Annual Report for 1898, published March, 1899.

the case is otherwise regarding codeine, as they say that "compared with codeine they (the acid derivatives) induce an equal narcotic effect with about one-tenth of the dose, while a dose about three times as large is necessary to cause tetanus. Their depressing action on motor nerves is about the same; the nausea and diarrhœa occurring in dogs is quite as great as after codeine." Thus as a substitute for codeine we might expect one of these substances to be of value. Quite recently Dreser,[4] on the strength of researches mainly on the respiration, has introduced diacetyl-morphine under the name of "heroin" into therapeutics. According to him it is more powerfully sedative and correspondingly less toxic than codeine; it lengthens the time of inspiration, increases the gaseous exchange, and does not affect the sensibility except in diminishing any tendency to over-extension of the lungs. So far the clinical results have supported Dreser's experiments, but as yet they have been too few to decide the position which this drug will hold in therapeutics. Von Mering says that di-acetyl-morphine, diproprionyl morphine, and di-benzoyl morphine diminish reflex irritability and the tendency to cough, but they are less effective as alleviators of pain than morphine. He believes that these substances are not suitable for practical use because they tend to decompose and do not form salts sufficiently soluble in water for hypodermic injection. But for this they were not recommended. Von Mering has found, on the other hand, that mono-acetyl morphine—in which the acetyl replaces the hydrogen of the alcoholic hydroxyl of morphine—is more sedative and less toxic than di-acetyl-morphine, and he states that he has used this substance with success in cases of advanced pulmonary tuberculosis in which codeine and di-acetyl-morphine had proved of little effect. "In a few cases its administration gave rise to stupor of the head, nausea, and constipation."[5]

The other derivative of morphine which has been introduced as a substitute is benzyl-morphine, the hydrochloride of which—$C_{17}H_{18}NO_2.O.C_6H_5.CH_2.HCl$—is called "peronin." This was introduced into practice by von Mering, who found it slightly less active than morphine but freer from ill effects. According to Schröder[6] it occupies pharmacologically a position between morphine and codeine, producing more restful sleep than the latter and no symptoms of stimulation. Moyer's more recent investigations[7] do not, however, support this statement. Small doses given to rabbits produced a certain amount of torpor, but the animals reacted to the least stimulus and if the dose was increased convulsions were produced. If artificial respiration was performed death resulted from cardiac paralysis. The lethal dose he found smaller than codeine, being in rabbits — peronin 0·023 gramme to 0·025 gramme, and codeine 0·063 gramme

[4] Pflüger's Archiv, Band lxxii., p. 455.
[5] Loc. cit., p. 10.
[6] Therapeutische Monatshefte, 1897, p. 4.
[7] Revue Médicale de la Suisse Romande, June 20th, 1898.

per kilogramme body-weight. My own investigations support these results. In a rabbit after a dose of 0·01 gramme per kilogramme injected intravenously convulsions occurred; in a rat (155 grammes) 0·02 gramme (0·13 gramme per kilogramme) injected into the peritoneal cavity produced depression, slow, deep respirations, clonic convulsions, and death in nine minutes. Codeine 0·0143 gramme given to a rat weighing 114 grammes (0·125 gramme per kilogramme) under similar conditions produced convulsions but was not fatal; but in one case 0·15 gramme per kilogramme caused death in eight minutes. Fish, too, are more susceptible to peronin than codeine, minnows dying sooner in 1 in 50,000 of the former than 1 in 7500 of the latter.

Stursberg[8] also appears to have found peronin more active than codeine and further removed from morphine pharmacologically, but, like myself, he also seems to have found it somewhat more sedative than codeine. From an experimental point of view, however, there seems little to recommend it in preference to codeine, as its increased sedative action does no more than counterbalance its increased toxic effect. But its true place in therapeutics must be settled by clinical observation and at present this is insufficient. It has not been used much as a hypnotic, but in the relief of pain and of the irritative cough of phthisis and chronic bronchitis it seems to have proved of value. Writing recently von Mering says that he has repeatedly satisfied himself of the excellent properties of this substance, but he regards its practical application as being limited partly on account of its sparing solubility (1 in 133) which makes it useless for injections and partly owing to its rather caustic taste.[9]

The other derivatives of morphine do not possess any practical interest. Chloromorphine, according to Stursberg, is allied in action to morphine; it possesses a narcotic effect and influences the respiration in a similar manner and in large doses it causes neither increase in the number of respirations nor the appearance of tetanus. He suggests its use in therapeutics. Previously Stockman had found that the chlorine derivatives of morphine, more particularly trichlor-morphine, acted in a similar manner on the nervous system to morphine, but he also found that they acted slightly as muscle poisons; tetanus followed their administration, but this was masked to some extent by the action of the drugs upon the motor nerves. On the whole, there seems no pharmacological reason for their introduction into therapeutics. An interesting point, and one with which I must close this part of my subject, in connexion with the influence of radicles introduced into morphine is the action of methyl codeine, $C_{17}H_{16}(CH_3)NO.OH.OCH_3$. In this substance a methyl group has been introduced into the parent nucleus of the morphine instead of into a side

[8] Ueber die Einwirkung einiger Abkömmlinge des Morphins auf die Atmung, Arch. d. Pharma., vol. iii.

[9] Merck's Annual for 1898, p. 12-13.

chain and according to Stockman the action of eodeine is completely changed. No narcosis or tetanus is produeed, but in their place paralysis of the voluntary muscles and depression of the spinal eord. It is therefore evident that we must look for no substitutes for morphine among its decomposition produets.

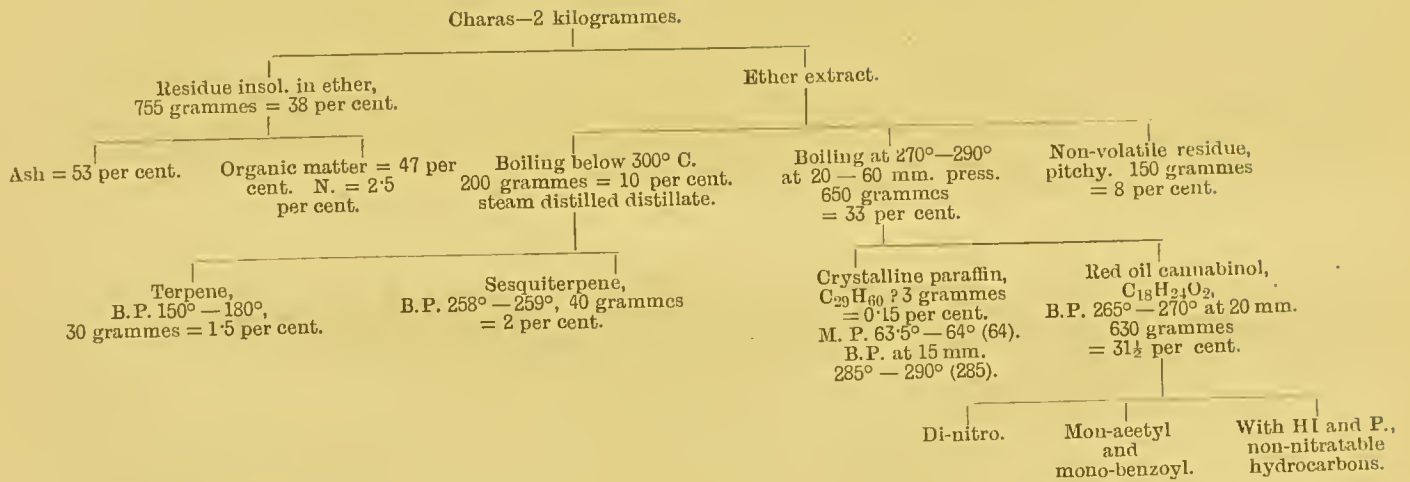
The drug next in interest to opium as a hypnotic is cannabis indica, and as the most reeent rcsearches on this substance have emanated from our Cambridge School I intend to dwell somewhat in detail upon it. Three years ago Messrs. Wood, Spivey, and Easterfield began to investigate the chemistry of this plant and as charas was its most active product they decided to work with this. Previously various substances had been stated to be the active principle. A resinous compound was isolated by O'Shaughnessy, Robertson, T. and H. Smith, and other more recent investigators ; an oily substance was obtained by Personne ; alkaloids by a few experimenters ; and to each of these the activity of Indian hemp was thought to be due. I will dispose of the alkaloids first. Many pharmacologists have thought that the effects of this plant would be found to depend upon a substance of this nature, mainly, it would appear, on account of its powerful physiological effects, but as yet this view has received little experimental support. Only minute quantities of an alkaloid have been found by some of the most recent workers and many have failed to obtain any. None was obtained by Wood, Spivey, and Easterfield from charas although it was carefully looked for. A pure alkaloid, cannabin finds a place in Merck's price-list, but although I have had it on order for some time it has not been obtainable. The firm states that recent samples of the drug have not contained any. As the alkaloid first isolated appears to have been nicotinc, and as most recent investigators have failed to obtain more than traces of an alkaloid and these not possessing the peculiar action of the drug, the hypothesis that the activity of Indian hemp is dependent upon this class of bodies must (for the present at least) fall to the ground. Personne's cannabene has been found to be an impure sesquiterpene and not the active principle, so I need say nothing more about it. We are therefore left with the resin, and all the most reliable observations point to this as the active substance. The brothers Smith appear to have obtained it in a fairly pure form more than half a century ago, and in reality little more was added to our knowledge of this substance until recently. In 1894 Leib Lapin[10] obtained by a very lengthy process a still purer substance which he termed "cannabindon," and still more recently the chemists at Cambridge isolated what was thought to be a pure substance and called it "cannabinol."[11] These investigators by extraction with various

[10] Dissertation, Jurjew.
[11] Journal of the Chemical Society, vol. lxix., p. 541.

solvents and subsequent distillation obtained several substances, as will be seen in the following table taken from the Cambridge Philosophical Transactions (vol. ix., p. 144). These substances, with the exception of the hydrocarbon, were passed on to my late assistant for pharmacological examination. He found that the resin cannabinol was decidedly active and produced most of the symptoms attributed to Indian hemp.[12] The terpenes, in much larger doses, had no such effect. In rabbits their administration was followed by slight excitement and in men by slight diuresis. These substances may possibly aid in increasing the rapidity of absorption of the active principle, but as far as the cerebral effect of Indian hemp is concerned this is probably all they do, and this only to a slight degree. The resin in doses of 0·1 gramme (1½ grains) produced marked intoxication, weakness in the legs, loss of memory, loss of time sensation, a peculiar tendency to laugh, a sensation of dryness of the lips, and an increased viscidity of the saliva. The pulse was increased in frequency and the pupils became slightly dilated. After smaller doses similar though less-marked effects occurred, but the limit was reached with 0·01 gramme, no distinct effect being produced by doses of this size. Sleepiness as an individual symptom was not always present, but there was always cerebral depression and sleep came more easily than under normal conditions. This was especially the case if the drug was taken in the evening. In dogs and cats similar symptoms were induced but proportionately much larger doses were required. Of the two species cats were the most susceptible. The symptoms were nervous depression, ataxia, anorexia, and sleep. In rabbits the only symptoms were slight depression, a fall in the frequency of the pulse and in the temperature. After very large doses death occurred.

As regards the time of onset of the symptoms in man these usually appeared about an hour after the administration of the substance, but the time depended to a great extent on the condition of the stomach; in one experiment the onset was delayed for three hours. This slowness of action is due to the comparative insolubility of the drug in aqueous media. In very dilute acids the resin appears to be quite insoluble; in dilute alkalies very slightly soluble. Marshall[13] believes that it is mainly in alkaline solution that it is absorbed and according to him the late appearance of the symptoms is partly due to the fact that the substance must ordinarily be passed on into the intestines before solution can occur. The very slight solubility of the resin is shown by the following experiment. Two Erlenmeyer's flasks were taken; into one (A) were put 2·127 grammes of cannabinol; into the other (B) 2·335 grammes of cannabinol. Both were left over sulphuric acid until they attained a constant weight. 100 cubic centimetres of a

[12] The Lancet, Jan. 23rd, 1897, p. 235.
[13] Journal of the American Medical Association, Oct. 15th, 1898.


Charas—2 kilogrammes.
Residue insol. in ether, 755 grammes = 38 per cent.
Ether extract.
Ash = 53 per cent.
Organic matter = 47 per cent. N. = 2·5 per cent.
Boiling below 300° C. 200 grammes = 10 per cent. steam distilled distillate.
Boiling at 270°—290° at 20 — 60 mm. press. 650 grammes = 33 per cent.
Non-volatile residue, pitchy. 150 grammes = 8 per cent.
Terpene, B.P. 150° — 180°, 30 grammes = 1·5 per cent.
Sesquiterpene, B.P. 258° — 259°, 40 grammes = 2 per cent.
Crystalline paraffin, $C_{29}H_{60}$? 3 grammes = 0·15 per cent. M. P. 63·5° — 64° (64). B.P. at 15 mm. 285° — 290° (285).
Red oil cannabinol, $C_{18}H_{24}O_2$, B.P. 265° — 270° at 20 mm. 630 grammes = 31½ per cent.
Di-nitro.
Mon-acetyl and mono-benzoyl.
With HI and P., non-nitratable hydrocarbons.

1 per cent. caustic soda solution were then added to A and a similar amount of 1 per cent. hydrochloric acid (anhydrous) to B. Both were shaken occasionally and left for 24 hours. The alkaline solution quickly became coloured; the acid solution remained clear. Finally, the liquid was poured off; in each case the residue rapidly washed and afterwards dried. The loss of weight in A was 0·03 gramme and in B 0·005 gramme, the latter being within the limits of experimental error.

Owing to the gradual loss of activity with age and perhaps other causes different preparations of cannabis indica often show marked variations in physiological activity. Even different specimens of cannabinol show a difference in physiological effect. To determine the cause of this various experiments were undertaken. Temperature in itself was found to have little influence, but the resin was found to be easily oxidised. When oxygen was passed through cannabinol, kept fluid by a temperature of 160° C., it rapidly darkened and after 19 hours the substance became very viscous and in cooling settled down to a brittle pitchy mass. On combustion this substance was found to be about half-oxidised cannabinol—that is, half the mass was probably unchanged from its original state. Given in the solid form this pitchy material was inactive probably because unabsorbed, but if previously dissolved in oil a distinct though feeble action was obtained. It is very probable therefore that the growing inactivity of Indian hemp is due to gradual oxidation, but this cannot at present be regarded as absolutely proved. Leib Lapin came to the same conclusion, but his proofs are less convincing than those of my late assistant.

We now come to the question of the active principle of Indian hemp. Is cannabinol the active ingredient? Marshall is inclined to think that it is, notwithstanding the fact that he got greater effects with spirituous and oily extracts of charas and with Merck's cannabinon. That the same symptoms are produced by cannabinol and the crude drug he thinks is an important point, and he suggests that diminished activity of the resin may be due to changes occurring during or subsequently to its manufacture, or to a diminished rapidity of absorption of the pure resin as compared with preparations of the crude drug. That cannabinol is the active principle was arrived at by a process of exclusion. All the other products, pure or impure, isolated from charas were inactive or much less active than this, and this being the case it is difficult to come to any other conclusion. At first the substance was thought to be pure; or if impure it was said that "the impurity could only be due to a stereo-chemical isomer or a compound with closely similar composition and properties." Since this was written the compound has been found to be composed of at least two substances, one having the empiric formula, $C_{21}H_{25}O.OH$ (to which the name cannabinol is now restricted),[14] the other

[14] Journal of the Chemical Society, vol. i., 1899, p. 20.

a lower carburetted compound not yet isolated in the pure state. The former substance was isolated by means of its acetyl compound which was obtained in a crystalline form. From this the cannabinol was obtained by de-acetylising. It presented nearly all the physical properties of the original substance, but it possessed scarcely any physiological activity. Whether the residual substance possessed greater physiological action has not been determined. So far it has been impossible to free it altogether of the higher compound, but probably this will be accomplished in course of time. At present the chemists have turned their attention mainly to the analysis of this new substance. From the old cannabinol by treatment with nitric acid they obtained a body previously isolated by Bolas and Francis and termed oxycannabin. This substance is a nitro-body and a lactone, and Wood, Spivey, and Easterfield propose the provisional name of "nitro-cannabino-lactone" for it. By successive conversion into the amido- and iodo-bodies these observers have obtained cannabino-lactone, and by subsequent treatment they have obtained from this iso-phthalic acid. From their analysis they have come to the conclusion that oxycannabin is nitro-meta-tolyl-butyro-lactone and thus has been established the first step in the determination of the chemical constitution of an active cannabis product. With the further determination of the constitution of these bodies, probably more light will be thrown upon the physiological activity of cannabis preparations and it is for this reason that chemical investigations of this kind are so important to the pharmacologist and therapeutist. Several derivatives of the original cannabinol have been tried physiologically, but none of these are of therapeutic interest. It was hoped to obtain a more soluble active product, but experiments in this direction have hitherto not been attended with success. Our present position, therefore, with regard to cannabis indica is this. We have obtained a more or less pure body with active physiological properties, but varying as regards these within rather wide limits. It has been thought that some connexion probably exists between the lightness of colour and transparency of the product and its physiological activity, but the interdependence of these factors has not been definitely determined. As alcoholic and oily extracts of charas are as active as, if not more so than, cannabinol, there seems to be some other undetermined factor unless the difference in effect is due to difference in absorbability. It seems probable that the loss of activity is due to gradual oxidation of the active principle and consequently all preparations should be kept as much as possible from light, heat, and air.

Other hypnotics derived from the vegetable kingdom which have aroused interest in recent years are hyoscine and pellotine and their allies. Hyoscine, as you know, belongs to the belladonna group of alkaloids, most of which are what Ladenburg termed tropcines. These are substances consisting of a base tropine united to an organic acid; atropine and hyoscyamine, for example, consist of tropine

united to tropic acid; hyoscine, another isomeride of atropine, of tropic acid united to pseudo-tropine. This drug has been said to be identical with scopolamine but the question is not yet settled. A number of other tropeines are known, most of them having been synthetically produced, but only one of these, homatropine, is of therapeutic importance and this mainly from an ophthalmological point of view. In this connexion it is interesting to note that when tropine, which is not very active physiologically, is combined with an aromatic acid it usually acquires active physiological properties. Thus tropine itself has no dilating influence on the pupil or marked action on the terminations of the vagus in the heart, but when combined with tropic or a similarly constituted acid all the atropine-like symptoms appear. It was at first thought that all aromatic acids possessing an alcoholic hydroxyl group when combined with tropine would induce this effect, but this is now known not to be the case. Hippuric acid affords us an example; hippuryl-tropine does not possess a physiological action like that of atropine. On the other hand, a few aliphatic tropeines, such as lactyl tropine, when given in large amounts produce an atropine effect—mydriasis and paralysis of the vagal terminations—and therefore, according to Gottlieb,[15] to whom most of our knowledge on this point is due, no conclusion can be drawn from the constitution of the tropeines as to their mydriatic or other actions.

As atropine and belladonnine and most of the other solanaceous alkaloids are not in themselves pre-eminently hypnotic, I shall not deal with them in these lectures. Hyoscyamine and hyoscine are the only ones we need consider. Both of these alkaloids, although so closely related to atropine chemically, are much more sedative to the brain. Hyoscyamine, as we have seen, possesses a similar composition, but it differs in optical activity and consequently to a slight degree in chemical structure; hyoscine differs from it slightly in chemical composition. Of the two hyoscine is the more sedative and the more reliable as a hypnotic. Indeed, it has almost totally replaced hyoscyamine for this purpose. The latter drug has often failed to induce sleep and it has produced more ill effects. As a type of the comparative effect of the two drugs we may take a series of cases reported by Wetherill.[16] He used the drugs in a series of mental cases and out of 268 administrations of hyoscyamine he only obtained a good night's rest in 73; in 68 a fair night's sleep followed and in 87 a poor one; and in 40 no sleep whatever was obtained. Thus in only 27·23 per cent. of cases was the result satisfactory; in 15 per cent. there was complete failure. Furthermore, unpleasant effects, such as dryness of the throat, vertigo, depression, and cardiac weakness, frequently followed. Hyoscine,

[15] Archiv für Experimentelle Pathologie und Pharmacologie, Band xxxvii., p. 218.

[16] American Journal of Insanity, vol. xlvi., p. 28.

on the other hand, in much smaller doses produced a good night's rest in 246 instances out of 348, and totally failed in only 14 cases. The ill effects also were less numerous, although of a similar kind. Serger's[17] results, however, are not quite so encouraging from a hypnotic point of view. Out of 914 administrations sleep was only produced in 11·5 per cent. of instances, although a calming effect was noted in 40 per cent. But there has been so much difference of opinion regarding the therapeutic value of this drug that it is difficult to come to any certain conclusions concerning it. In the published cases there has been so wide a variation in the dose that one is drawn to the conclusion that in many cases impure preparations have been used, and the same remark applies to experimental investigations; different observers have obtained very different results. From a chemical point of view Schmidt and Hesse have maintained that commercial hyoscine is not pure; that it is not hyoscine, but an impure scopolamine. This substance is not a tropeine but a scopoleine; instead of being broken up into tropic acid and tropine it is decomposed into tropic acid and scopoline; but this question of the identity of hyoscine and scopolamine cannot be regarded as settled. Ladenburg still maintains their individuality. Hyoscine hydrobromide, however, at first introduced into the German pharmacopœia, has been replaced by scopolamine hydrobromide and Kobert from pharmacological investigations has maintained their identity. Rotislaw,[18] a pupil of Kobert, has also given support to this view. But hyoscine seems to be slightly more powerful than scopolamine and this makes it rather difficult to accept the identity of the two. The most recent investigator, H. de Stella,[19] gives the relative toxicity as scopolamine, one; hyoscine, two; and atropine, seven; and he also describes a different effect on the circulation of the dog. Both drugs cause a rise of blood-pressure, but scopolamine is said to produce this by increasing the number of heart beats and hyoscine by stimulating the vaso-constrictor centre. But I doubt if stress can be laid on the latter condition and for the present the question must be left unsettled. There can be little doubt, however, notwithstanding the many ill effects attributed to its use and to its variable action, that hyoscine or scopolamine as a hypnotic has come to stay. For the treatment of insomnia in general it will probably never come into use, but its solubility in water and its applicability to hypodermic medication make it of extreme value in many conditions, particularly in the insane. In exhaustion from any cause and in advanced heart disease it is said to be contra-indicated.

The other drug which I have mentioned is pellotine. It is an alkaloid derived from the Anhalonium Williamsii and it was suggested as a hypnotic only a few years ago. There

[17] Allgemeine Zeitschrift für Psychiatrie, Band xlvii., p. 322.
[18] Dissertation, Dorpat, 1893.
[19] Archives de Pharmacodynamie, tome iii., p. 385.

are two species or varieties of Anhalonium which have attracted attention during the last few years—Anhalonium Williamsii and Anhalonium Lewinii, or Meseal button. These have been investigated most extensively by Heffter.[20] He isolated pellotine from the Williamsii and mescaline, anhalonidine, anhalonine, and lophophorine from Anhalonium Lewinii. Mescaline in frogs produced decided cerebral depression and lophophorine distinct stimulation. Between the two in action are arranged pellotine, anhalonidine, and anhalonine. In these a narcotic stage is followed by a tetanic one. Anhalonidine produces the most prolonged narcosis and anhalonine the shortest. In warm-blooded animals, however, these effects were not observed and in experiments on himself no marked narcosis was produced. Anhalonidine (0·1 gramme to 0·25 gramme—1½ to 3¾ grains) caused some sleepiness and heaviness of the head, and anhalonine (0·1 gramme—1½ grains) produced slight sleepiness, but neither of these seem likely to prove useful as hypnotics. Pellotine is the only one of these alkaloids which has been put to practical use and this in only a few instances. This substance does not appear to be on the market. I have endeavoured to get some both for experimental investigation and therapeutic use but have failed. Jolly[21] and Pilcz[22] have recorded cases treated by this drug. In 58 administrations Pilcz obtained from one-third of a grain a satisfactory night's rest in half the cases; in 21 per cent. it failed. Jolly had to use larger doses and in excitable and delirious patients he only obtained a calming effect. Giddiness was also complained of. He gives its relative strength as pellotine 0·06 gramme; trional, one gramme; chloral hydrate, two grammes; and in conclusion states that the number of cases is too small to justify an opinion, but it deserves further trial. This, as far as I am aware, has not been forthcoming. Wilcox[23] is inclined to believe that it may be of considerable value.

There are still other drugs possessing hypnotic properties, such as Jamaica dog-wood and the various species of lettuce, but as these are not of much value and are but little used in the present day I shall pass on to the next division of my subject.

The Treatment of Insomnia.

This, notwithstanding its apparent simplicity, is one of the most difficult subjects in therapeutics. On the one hand, we have a series of drugs which given in sufficient doses will, we know, in the majority of cases produce a desired result; on the other hand, apart from any immediate ill-effects, we may make our patient a slave to a habit which in the long

[20] Cf. Archiv für Experimentelle Pathologie und Pharmacologie, Band xl., p. 383.

[21] The Lancet, June 20th, 1896, p. 1760.

[22] Heffter: Archiv für Experimentelle Pathologie und Pharmacologie, 1894.

[23] Brit. Med. Jour., vol. ii., 1897, p. 856.

run will prove more disastrous than the insomnia itself. In the first lecture I expressed an opinion that drugs were often valuable in the treatment of sleeplessness, but I now hasten to add that they should never be used in a routine manner. In the case of insomnia the first great principle of therapeutics—the removal of the cause—should ever be kept in mind, the relief of the symptom being regarded as secondary to this. It is therefore necessary to inquire first into

The Causes of the Insomnia.

But before dealing with this question a preliminary one—what constitutes insomnia?—must first be answered. For what is sleeplessness to one person may not be so to another. The average sleeping time of an adult is from six to eight hours, but Brunel and Alexander von Humboldt, and others I could mention, required much less time than this; other well-known men needed more. The amount of sleep, therefore, varies with the individual. It also varies with age. Infants sleep the greater part of their time. As they grow older gradually less sleep is required until adult life is reached; with the onset of old age more sleep is again needed. The amount of sleep varies, too, with the mental constitution of the individual—idiots and persons of weak intellect often sleep excessively—and with the quality of the sleep, profound and continuous sleep being much more refreshing than superficial and broken. Considering these variations insomnia may, perhaps, best be defined as a loss of the normal amount of sleep. This loss may occur at the beginning or towards the end of sleep or it may occur through constant awakenings. Thus some people go to sleep directly after getting into bed but awake every hour for several hours, sleeping well the rest of the night. Others, especially the gouty, awake punctually at 3 o'clock or 4 o'clock and are unable to sleep again, or, at any rate, until it is time to get up; others, as I have said, find great difficulty in getting off, but once asleep do not awaken until the morning. Occasionally, even, we see patients who assert that they do not sleep at all—a statement which must usually be accepted with reservation, although, as a rule, such cases are of serious omen.

Returning now to the causes of insomnia we shall find that they may be classed under four heads: (1) irritative causes; (2) toxic causes; (3) psychical causes; and (4) causes arising from change in the mode of life. Others have classified them differently. Germain Sée, for example, recognises nine divisions: dolorous, digestive, cardiac and dyspnœal, cerebro-spinal and neurotic, psychic, insomnia of cerebral and physical fatigue, genito-urinary, febrile, and toxic. This it will be seen is a symptomatic classification and does not bring us any nearer to the true causes of insomnia. The one I have adopted is simpler and, I think, more in accordance with etiological factors.

1. *Irritative causes.*—This class includes all forms of insomnia caused by pain and milder irritations, like uneasiness. In children teething, indigestion, worms, and so forth are frequent causes. Eye-strain—as in hypermetropia and astigmatism—the irritation of an eczema, the inconveniences produced by faucial adenoids and other similar conditions, are also etiological factors of insomnia. After surgical operations, even in the absence of pain, insomnia is not infrequent; and this may be due in part to the constrained position of the patient and some irritability of the wound and in part to toxæmic and psychical causes. Cold feet, vesical affections, asthma, bronchitis, and other diseases accompanied by troublesome, if slight, irritations — for example, cough or local and general pruritus—fall under this head. But the most important causal factor of this group is undoubtedly pain. In all diseases accompanied by pain—as neuralgia, sciatica, migraine, angina pectoris, aneurysm, locomotor ataxy, the various forms of colic, acute inflammation of the serous membranes (peritonitis, pleuritis, pericarditis, and meningitis), cerebral tumours and abscesses, malignant growths in various parts, diseased bone, acute and chronic rheumatism, osteo-arthritis, syphilis (the pains of which are often worse at night), and acute gout—sleeplessness is a symptom. All or many of these may include other etiological factors of insomnia, but the pain is the predominant one and is that which necessitates treatment.

2. *Toxic causes.*—A large number of diseases are due to, or are accompanied by, the presence of some toxic agent in the blood and such diseases are often attended by troublesome insomnia. Alcoholism and nicotism, the exanthems (measles, small-pox, and scarlet fever), enteric and other continued fevers, erysipelas, diphtheria, pneumonia, hepatic disorders (the lithæmia of Murchison), dyspepsia, and other gastric and intestinal disorders, rheumatism, gout, and Bright's disease are some of the conditions which may be mentioned under this head. The insomnia accompanying heart disease and altered vascular conditions (arterio-sclerosis, &c.) may also be included in this division, as its origin in most of such instances appears to be a blood poison. This form of insomnia is also partly due to a deficient blood-supply and possibly to an altered cardiac action. The sleeplessness induced by certain beverages, such as tea, coffee, and cocoa, requires mention here. These, especially if taken in a strong form and late at night, are powerful preventives of sleep in most people. Strychnine and other nervine tonics when taken regularly often cause sleeplessness during the earlier part of the night, but in certain conditions by improving the circulation and other functions they prove excellent hypnotics. Insomnia is also a symptom of certain drug habits, such as opium eating, morphinism, and cocainism.

3. *Psychical causes.*—Grief, shock, worry, and mental

anxiety are among the most frequent eauses of insomnia. In many persons a predisposing faetor—a nervous temperament, neurasthenia, hysteria, or hypochondriasis—also exists and among such persons insomnia may easily be established as a habit. In students, overwork, espeeially if aeeompanied by irregularity in retiring to rest and the prospect of an examination, are the most frequent eauses. Women at the menopause often suffer from insomnia, partly, perhaps, owing to the aeeumulation of toxie produets not eliminated by the eatamenia. The various forms of insanity, such as mania, melaneholia, and general paralysis, are aeeompanied by insomnia, usually as a premonitory symptom, but there ean be no doubt that eontinued loss of sleep is also a faetor in the produetion of mental aberrations. Cases of severe chorea and of paralysis agitans are also marked by sleeplessness.

4. *Causes arising from change in the mode of life.*—Eating late dinners by those unaeeustomed to them and change of climate, espeeially to high altitudes or in some individuals even to the seaside, sometimes give rise to temporary insomnia. Nurses who have been on night duty after changing to the day frequently suffer from sleeplessness; and the same condition oeeurs in other people with intermittent noeturnal oeeupations. Sometimes very simple changes in the mode of life of individuals will lead to insomnia. A patient under my eare and his wife both slept very badly for the first three months after beginning to cycle. This may have been due to exeessive fatigue or possibly to inereased waste produets in the blood or to both eombined.

It is evident from the multiplieity of these causative factors that no one line of treatment can be suitable for all cases. As I have said, the first thing to do is to "remove the cause," therefore the treatment of insomnia resolves itself primarily into the treatment of the eausative eondition. If it is indigestion, acid or gouty dyspepsia, eareful attention to the diet, the avoidanee of tea and cooked or uneooked fruit, and of all substanees eontaining vegetable aeids, except in so far as these may be used in treatment, are essential. Fruit, owing to the acid it eontains, is, I believe in many individuals, an unsuspected eause of indigestion, gout, and sleeplessness, and so are aeid wines. In the gouty mueh butcher's meat, espeeially beef, should be prohibited, and white fish, poultry, and game should be taken in its plaee. Fried fat sueh as that on the outside of fried fish should also be avoided. An alkaline bitter before meals, an oeeasional mereurial at bedtime, followed by a saline aperient the next morning, and in the gouty eolchieum and magnesia or sodium salieylate should be prescribed. Sometimes a dose of Gregory's powder at bedtime or a mild carminative is of value. One of my patients found that a little peppermint water taken at bedtime gave him a better night than any hypnotie. In the

insomnia of the aged and the overtired, and in that due to cardiac and vascular disease, nux vomica and strychnine are beneficial remedies. They tone up the circulatory system, remove indigestion and flatulence, and act directly on the cerebral cells. In cardiac disease and in neurasthenics with low arterial tension digitalis and the other cardiac tonics may be resorted to. In anæmia iron, nux vomica, and sometimes digitalis, are required; and in a similar way other diseases which are causal factors of insomnia must be treated. But often this method does not suffice. The removal of the cause does not bring back refreshing sleep. The reason is that the cerebral cells have assumed an irritable condition, and it is necessary to depress their activity to bring them back to a more normal state. In other words, we have to break the habit of sleeplessness; and it is here that hypnotics are of such great value. The best of these for any individual patient will vary according to his condition. There is no absolutely safe hypnotic, but experimental investigation and clinical experience show that paraldehyde stands in the first rank. Chloralamide and chloralose are safer but slower in action than chloral hydrate, and of the two I decidedly give the preference to chloralamide. The sulphones are also valuable and in practice I have found sulphonal the most valuable of the three. But as a whole the bromides seem to be the least harmful and in simple cases, uncomplicated by other diseases, it is my practice where I think a hypnotic is necessary to try them before resorting to any other drug.

But leaving these general indications and coming to the special therapeutics of insomnia we may divide this into non-medicinal and medicinal. The first of these, as it is more or less common to the treatment of all insomnias, I shall deal with first. In all cases, where practicable, the bedroom ought to be in a quiet part of the house, well ventilated, and of moderate temperature. Light should be easily excluded and the apartment scantily furnished. The bed should vary according to the custom of the individual—for young and middle-aged adults a firm mattress is the best, but for the old a softer bedding may be necessary. The covering should be light and warm, but in the use of pillows no general recommendation can be made. Some people sleep better with the head raised, others with the head on a level with the body. In heart disease it will be found necessary to raise it; but as a rule this arrangement may be left to the choice of the individual. For broad-shouldered people Whitla recommends the wedge-shaped pillow used by the Germans. Some invalids find much refreshment from the use of two beds—one for the day and the other for the night. In individual cases various means must be resorted to for the purpose of inducing sleep and often simple ones suffice. Thus some people read themselves to sleep, some people count, other people, like Southey, think of some monotonous

discourse. One of my patients used to hang his feet out of bed for some time and then put them in again. Walking about naked or taking a cold or tepid bath is often useful. Massage, especially of the abdomen, the thighs, and the legs, as in Dr. Eccles's method of treating insomnia, is sometimes advantageous. This method is believed to produce temporary anæmia of the brain by causing a determination of blood to the manipulated parts and it may be further aided by a hot compress to the abdomen. In the case of cold feet rubbing them vigorously or the use of a hot bottle or a footbath with mustard in it is beneficial; or, again, a hot sitz-bath may be used. Attention should also be given to the condition of the stomach. As a rule a light supper is the best and for many, and especially those who awake in the middle of the night, a little hot milk or meat juice containing a small amount of alcohol is helpful. The evacuations should also be attended to and the bladder especially be relieved.

Sleeplessness from overwork, and especially literary work, requires mental rest and change of air and scene. Temporary exposure to the cool air of the bedroom or the wet pack or a bath is often of use, and so is a glass of whisky-and-water at bedtime, especially in those unaccustomed to the use of alcohol; but if the insomnia continue it is necessary to give a mild hypnotic, such as 20 grains of sulphonal or 30 or 40 grains of bromide of potassium, to break the habit of sleeplessness. Capsules containing 30 minims of turpentine given at bedtime are sometimes beneficial in the insomnia of overwork and worry. The drug acts as a stimulant and derivative and is stated to be most successful in plethoric cases. No beverages containing caffeine should be taken after breakfast.

In nervous and hysterical women, and especially in women at the menopause, the bromides are very useful. I have long been in the habit of giving a mixture of bromide—either of potassium, sodium, or ammonium—tincture of sumbul, and tincture of hop, in camphor water at the climacteric; and it has helped to remove the insomnia as well as the mental depression and flushing heats so common at this period.

The sleeplessness of the insane requires careful management. In the early stages of acute mania the bromides, chloral, hyoscine hydrobromide, and other sedatives are useful, but a hot bath at a temperature of 104°F. and cold water simultaneously poured upon the head are most efficacious in inducing sleep. In melancholia, where arterial tension is usually high, paraldehyde in doses of from 40 minims to 90 minims or even more is a valuable hypnotic, and so is morphine, but a 1-grain dose of erythrol tetranitrate by reducing arterial tension will frequently act better than anything else. In mild cases of delirium tremens sleep usually comes on after a time whatever treatment be adopted; in the more severe cases chloral and bromides, alone or in combination, are beneficial. Paraldehyde is re-

commended by some physicians. Opiates may be given, but in most cases hyoscine is probably a more efficient remedy. Among the medical officers of the American army 20 grains of powdered capsicum in the form of a bolus is the favourite hypnotic for this complaint. I have had no practical experience of this prescription and cannot therefore express any opinion of its value as a mode of treatment. Cerebral depressants should be given as little as possible and the treatment should be confined chiefly to feeding and tonic measures.

In pneumonia sleep usually comes at the crisis, but where this has not occurred I have occasionally seen a hypnotic—such as chloralamide or paraldehyde—turn the scales in favour of the patient. In pleurisy and most other serous inflammations from five to 10 grains of Dover's powder usually conduce to sleep mainly by relieving the pain. A hypodermic injection of morphine may be given with the same object in view. In bronchitis chloral and chloralamide are safe hypnotics and, as a rule, opiates are to be avoided, as these, as I have pointed out, depress the respiratory centre. The sleeplessness of asthma is relieved by remedies which cut short an attack, such as chloral hydrate, the fumes of Himrod's and other asthmatic powders, the hypodermic injection of morphine, or in some cases from a five-grain to a 10-grain dose of citrate of caffeine. Bromides are also useful and so is paraldehyde, which both relieves the asthma and causes sleep. A change of locality even to another part of the same town often succeeds. In one case the removal of a student from Downing College, Cambridge, to a house across the street brought relief and in another of my pupils the change from Caius College to a house in another part of the town brought to an end a most troublesome attack of asthma with its attendant sleeplessness.

The insomnia of heart disease is benefited by digitalis, strophanthus, strychnine, and other cardiac tonics, but in some cases it is necessary to resort to morphine either by the mouth or, still better, hypodermically, as first suggested by my colleague Professor Allbutt. Paraldehyde and chloralamide are in my experience most useful. Ice to the head is recommended by Morison where the vital forces are not too low or the temperature subnormal. It often produces sleep rapidly with a more regular cardiac action. Heat may possibly answer in other cases presenting a subnormal temperature. In chronic Bright's disease insomnia is occasionally very troublesome. Eliminants such as aperients should be tried and if they do not succeed chloral hydrate may be given. The drug is safer in kidney than in heart disease, the reduction of blood-pressure being usually beneficial than otherwise. Morphine and hyoscine hydrobromide subcutaneously injected have been recommended in obstinate cases, but their employment requires great caution. Erythrol tetranitrate, by reducing arterial tension, often acts as a charm even when sedatives have failed; and in one of my patients thorough rubbing of the skin by means

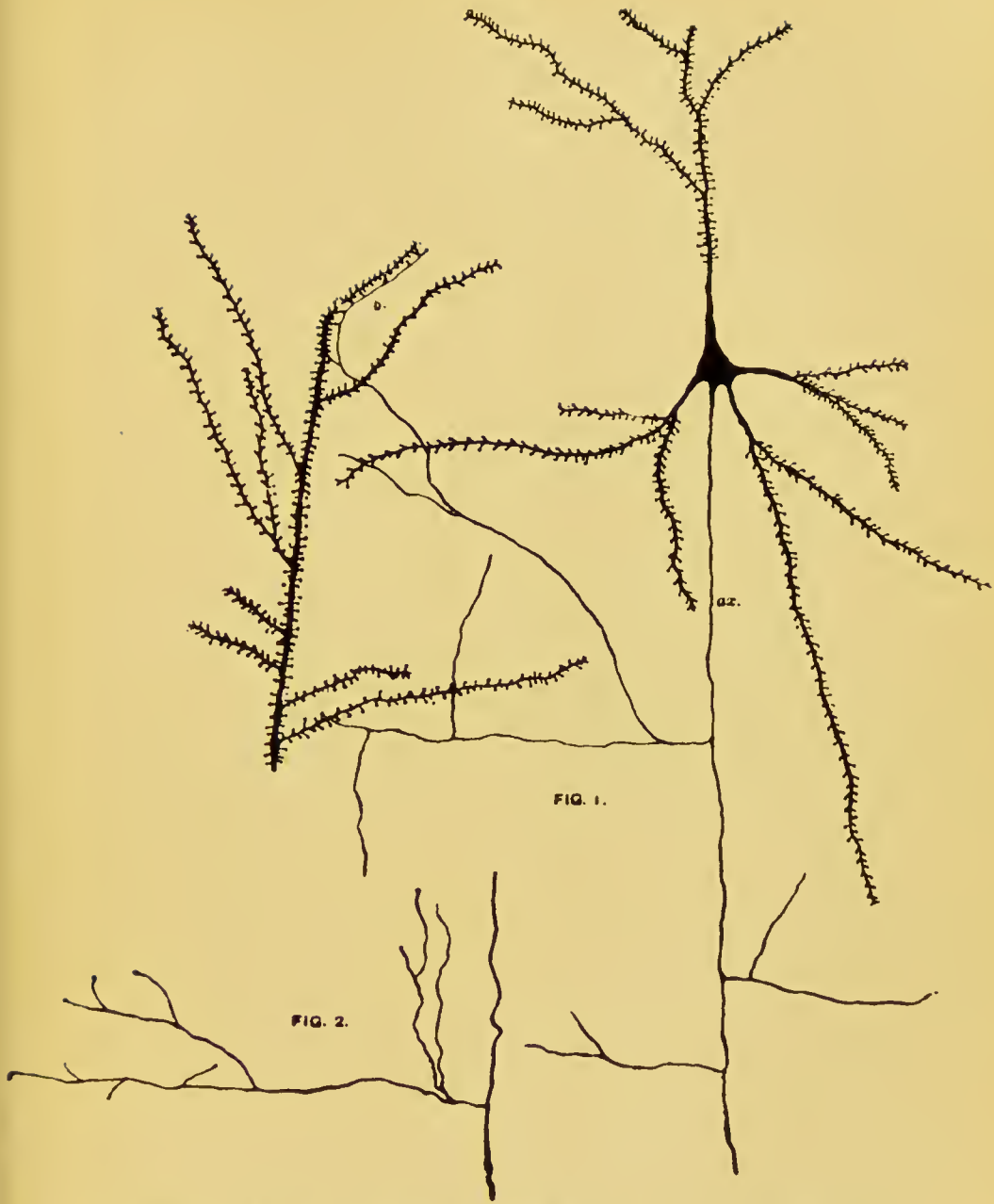
of a flesh-brush induced sleep and very materially relieved the restlessness of the disease. When pain is the causal factor of insomnia morphine is usually the best remedy and this should be pushed until relief is obtained. In cases of neuralgia, locomotor ataxy, and so forth, some of the synthetic analgesics—phenazonum or phenacetin—are of value. These drugs, as I have previously stated, act also as hypnotics in cases where there is no pain. Calcium chloride is a valuable remedy in the insomnia due to pruritus.

In conclusion I must again thank you, Mr. President and Gentlemen, for the patience and attention with which you have listened to these lectures. The subject I have chosen is a most difficult one and required a much abler head than mine to deal satisfactorily with it. Nobody is more conscious than myself of the imperfection of what I have presented to you, but, as I observed at the beginning, the subject of sleep, sleeplessness, and hypnotics has for some time occupied my attention, and although I may have had nothing particularly novel to say I hope that my remarks will at any rate stimulate some of my younger hearers to extend our knowledge of the subject.

FIG. 1.

The principal types of cells of the cerebral cortex in mammifera. A, Pyramidal cell of medium size. B, Pyramidal giant cell. C, Polymorphous cell. D, Cell of which the axis cylinder is ascending. E, Cell of Golgi. F, Cell peculiar to the molecular layer. G, Fibre ending freely in the substance of the cortex. H, White matter. I, Collateral of the white matter. (After Ramón y Cajal.)

FIG. 2.



The figure is made up of two figures. (After Berkley.) Fig. 1, Psychical neurons, showing the end-apparatus of a collateral situated against the dendrite of another cell. Human. Fig. 2, Form of termination of the ascending fibres of the cortex. Guinea-pig.

Description of Fig. 3.

This figure is made up of eight small figures. (After Vas.)

Fig. 1, *a*, Normal anterior cornual cell of the spinal cord of the rabbit; *bb*, the same of the spinal cord of the dog.

Fig. 2, *a*, Normal spinal ganglion cell of the dog; *bb*, Normal spinal ganglion cell of the rabbit.

Fig. 3, Normal ganglion cell of the first cervical sympathetic nerve of the dog.

Fig. 4, *a*, Anterior cornual cell poisoned with alcohol in a dog; stage of partial degeneration; *b*, Anterior cornual cell poisoned with alcohol in a rabbit; stage of partial degeneration; *c*, Anterior cornual cell poisoned with nicotine in a rabbit; stage of partial degeneration.

Fig. 5, Small granular disintegration of the chromatine structure. *a*, Alcohol dog; *b*, Alcohol rabbit; *c*, Nicotine rabbit.

Fig. 6, Anterior cornual cell in the stage of homogeneous swelling. *a*, Dog; *b*, Alcohol rabbit; *c*, Nicotine rabbit.

Fig. 7, Disintegration and homogeneousness of the chromatine structure of the cells of the sympathetic ganglion (first cervical). *a*, Nicotiue rabbit; *b*, Alcohol rabbit.

Fig. 8, The same in the cells of the spinal ganglion of the rabbit. *a*, Nicotine; *b*, Alcohol.

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FIG. 3.

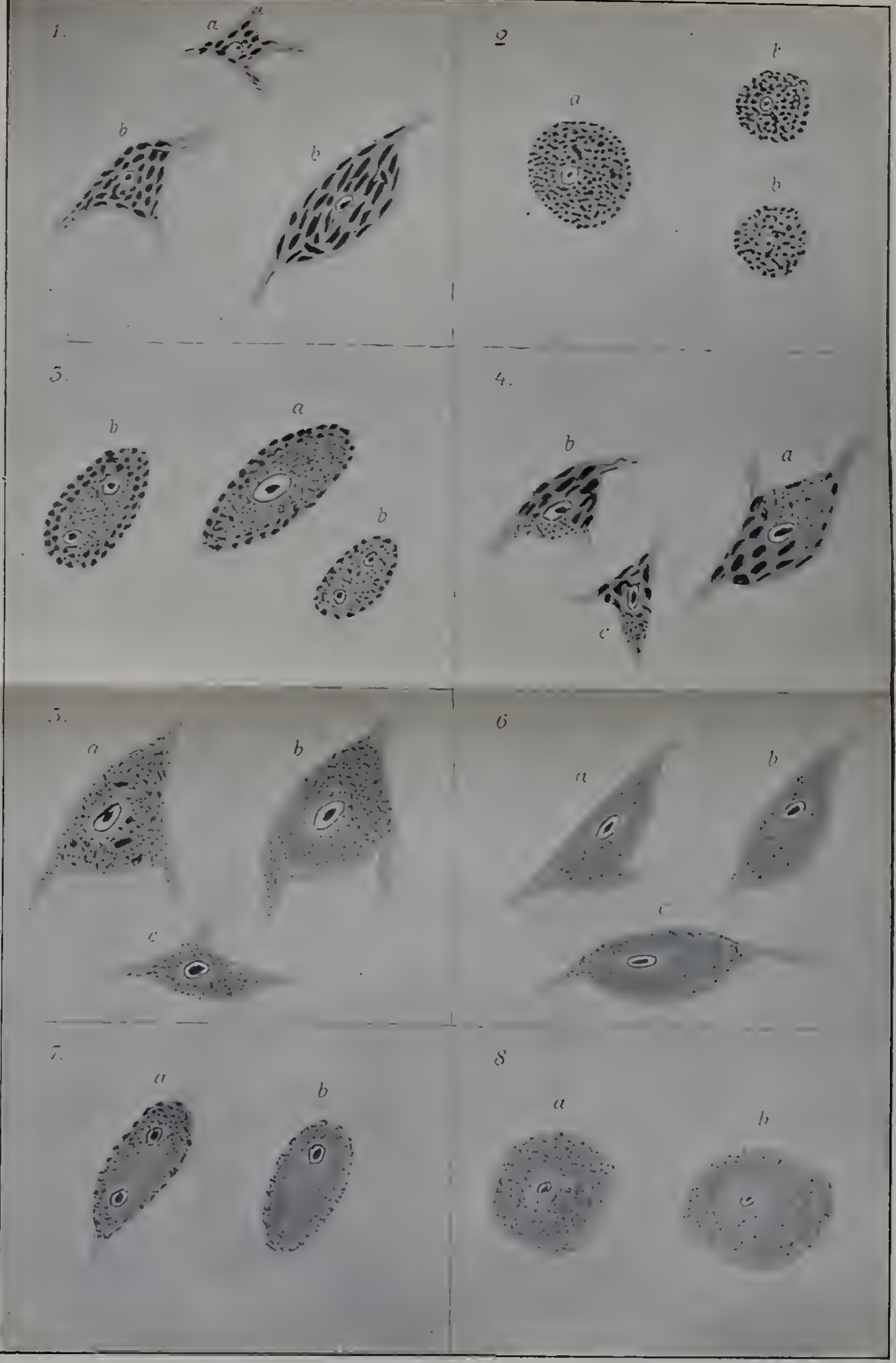
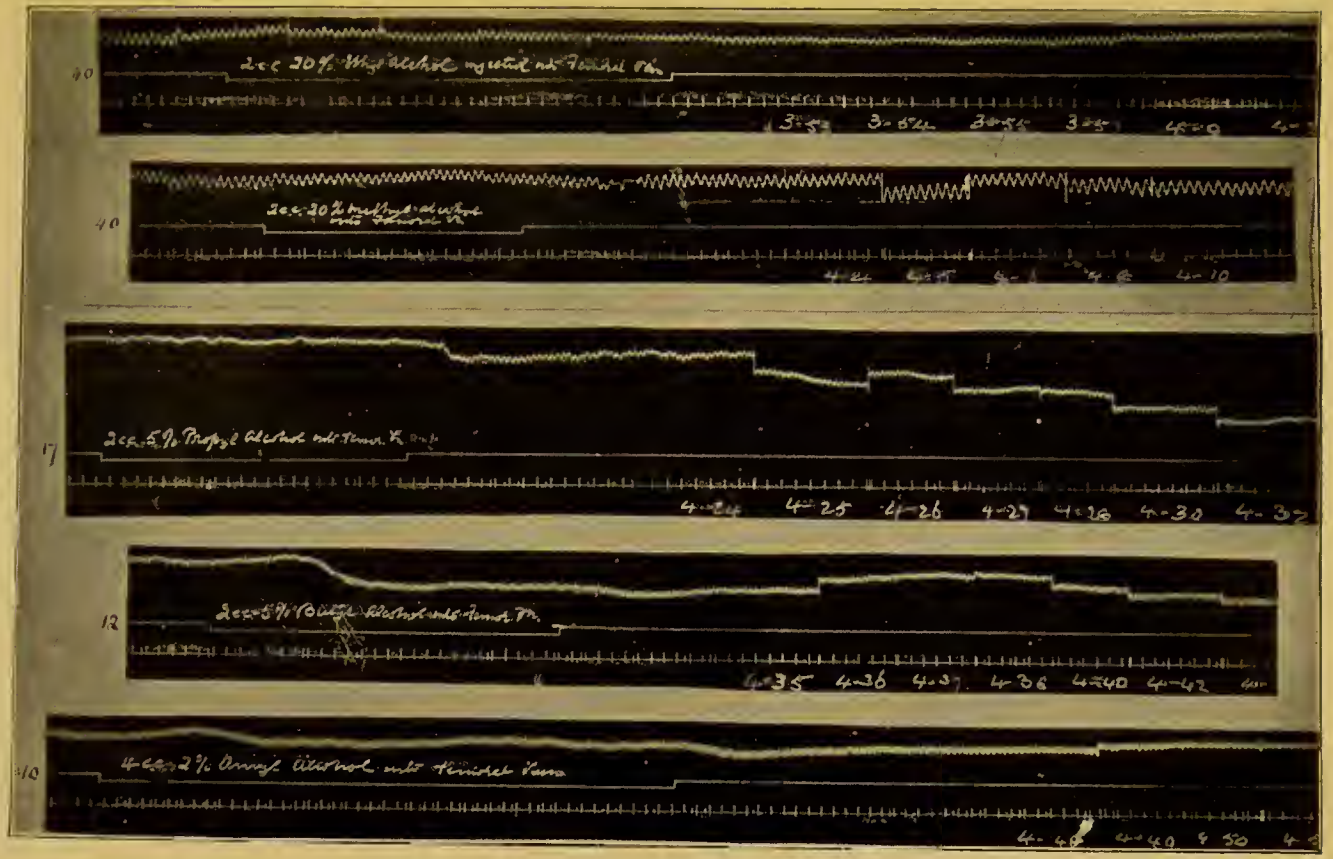


FIG. 4.



Comparison of the effects of different alcohols upon blood-pressure. (*The effect of amyl alcohol is not well shown in the tracing.*) *Rabbit weighing 2380 grammes. Chloroform-ether. Tracing from carotid artery. Injections into femoral vein. Base-line raised: indicated by numbers (= mm.) at side. Time marks, two seconds.*

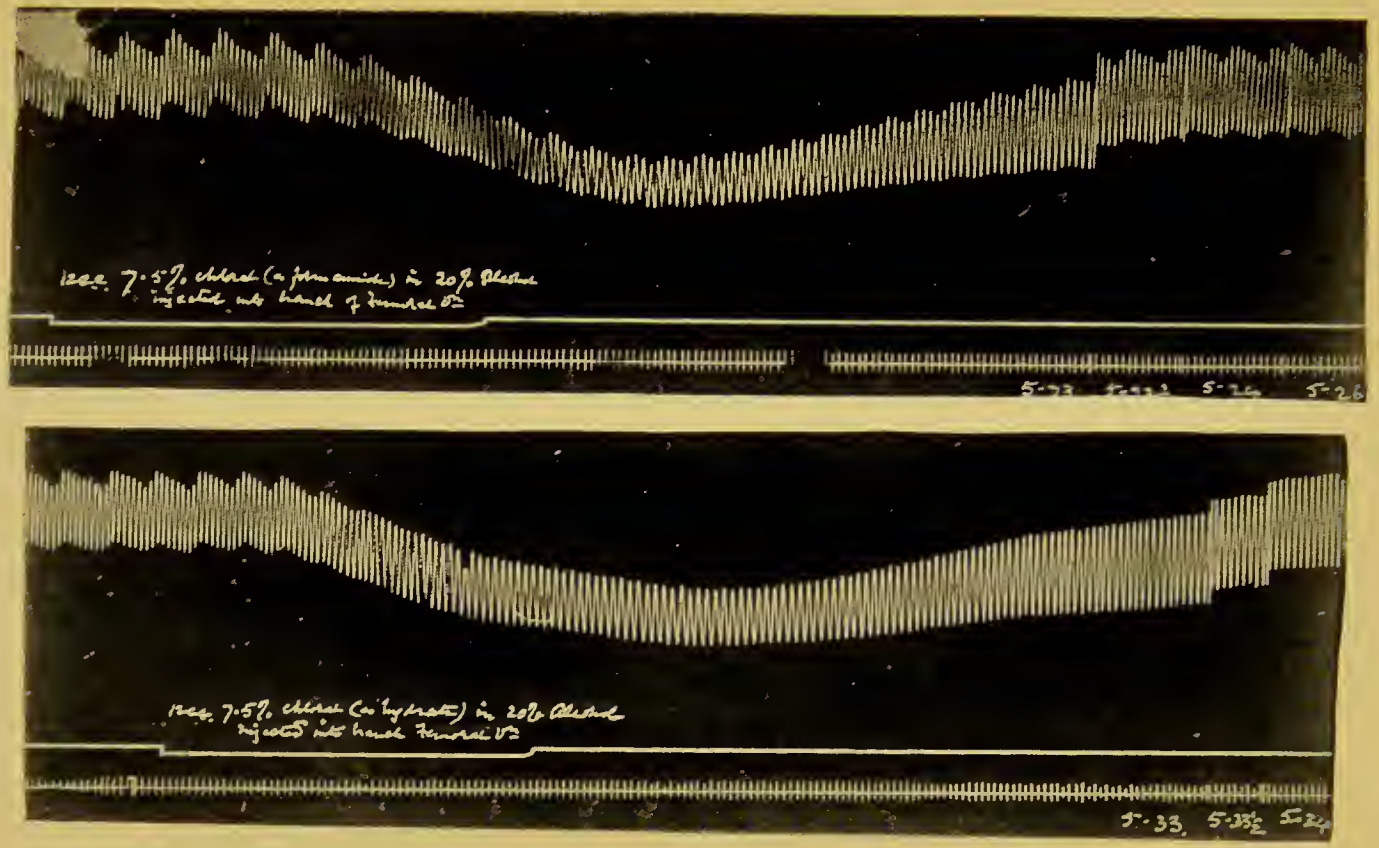
FIG. 5.

Comparison of effect of methylal and acetal on blood-pressure. *Rabbit weighing 1430 grammes. Chloroform. Tracing from carotid artery. Injections into femoral vein. Base-line raised 20 mm. and 10 mm. respectively. Time marks, seconds.*

FIG. 6.

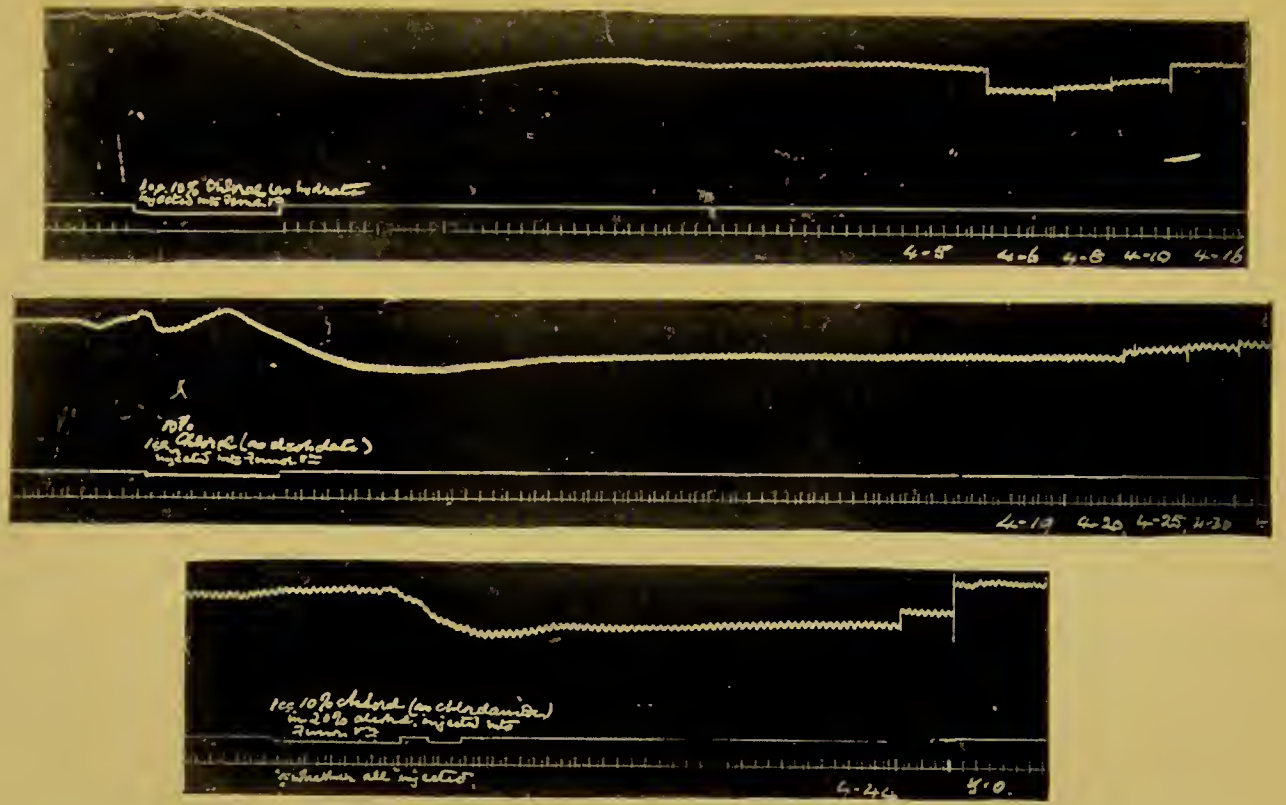
Comparison of the effects of chloralamide, chloral hydrate, and chloral alcoholate upon blood-pressure. *Dog weighing 9040 grammes. Morphine-chloroform. Tracing from carotid artery. Injections into femoral vein. Base-line raised 40 mm. Time marks, seconds. Same amount of chloral injected in each case.*

FIG. 7.



Comparison of chloralamide and chloral hydrate on blood-pressure. *Dog weighing 9040 grammes.* (*Same animal as Fig. 6.*)

FIG. 8.



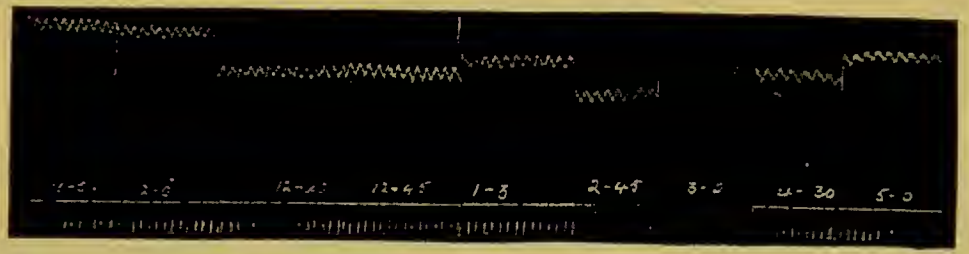
Comparison of the effects of chloral hydrate, chloral alcoholate, and chloralamide upon blood-pressure. *Rabbit weighing 3430 grammes. Ether as anæsthetic. Tracing from carotid artery.*

Effect of Chloral Hydrate and Chloralamide, used as Anæsthetics, on Blood-pressure.

Fig. 9 A.

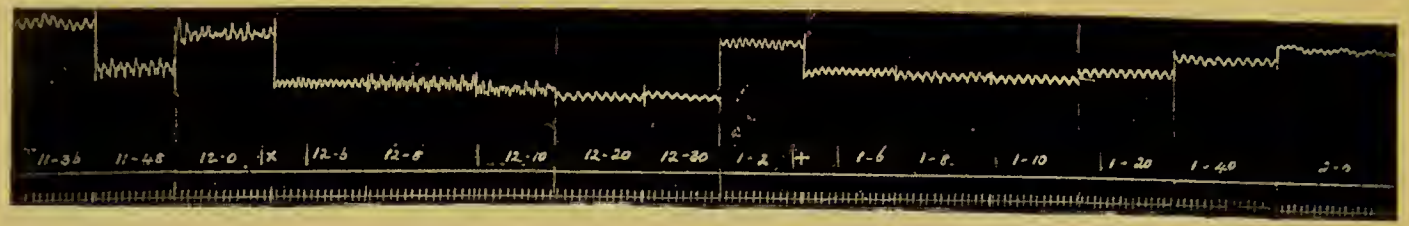
Rabbit weighing 1720 grammes. (P. 156. R. 120. T. 38·5.) 2.34 : 1·92 grammes chloral hydrate (= 1 gramme per kg. Chloral) in 20 c.c. H_2O injected into stomach. 2.49 : Well under ; no corneal reflex. (P. 252. R. 42.) Operation commenced.

Fig. 9 B.



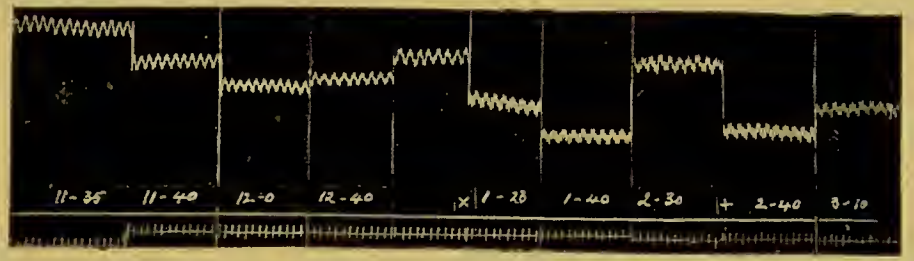
Rabbit weighing 1730 grammes. (P. 240. R. 130. T. 39·2) 10.25 : 2·25 g. chloralamide (= 1 gramme per kg. chloral) as emulsion injected into stomach. 11.30 : Operation commenced. (P. 238. R. 60.) Not so deeply under as in previous case.

FIG. 10 A.



Chloral hydrate. *Rabbit weighing 1800 grammes. (P. 276. R. 86.) 11.15 : 5 c.c. $\frac{1}{30}$ chloral (as hydrate) injected into marginal vein of ear. 11.20 : 2½ c.c. ditto. 11.23 : 2½ c.c. ditto. 11.25 : Operation commenced. × 12.4 to 12.6 : 5 c.c. $\frac{1}{30}$ chloral (as hydrate) solution injected. + 1.3 to 1.5 : 5 c.c. $\frac{1}{20}$ chloral (as formamide) injected.*

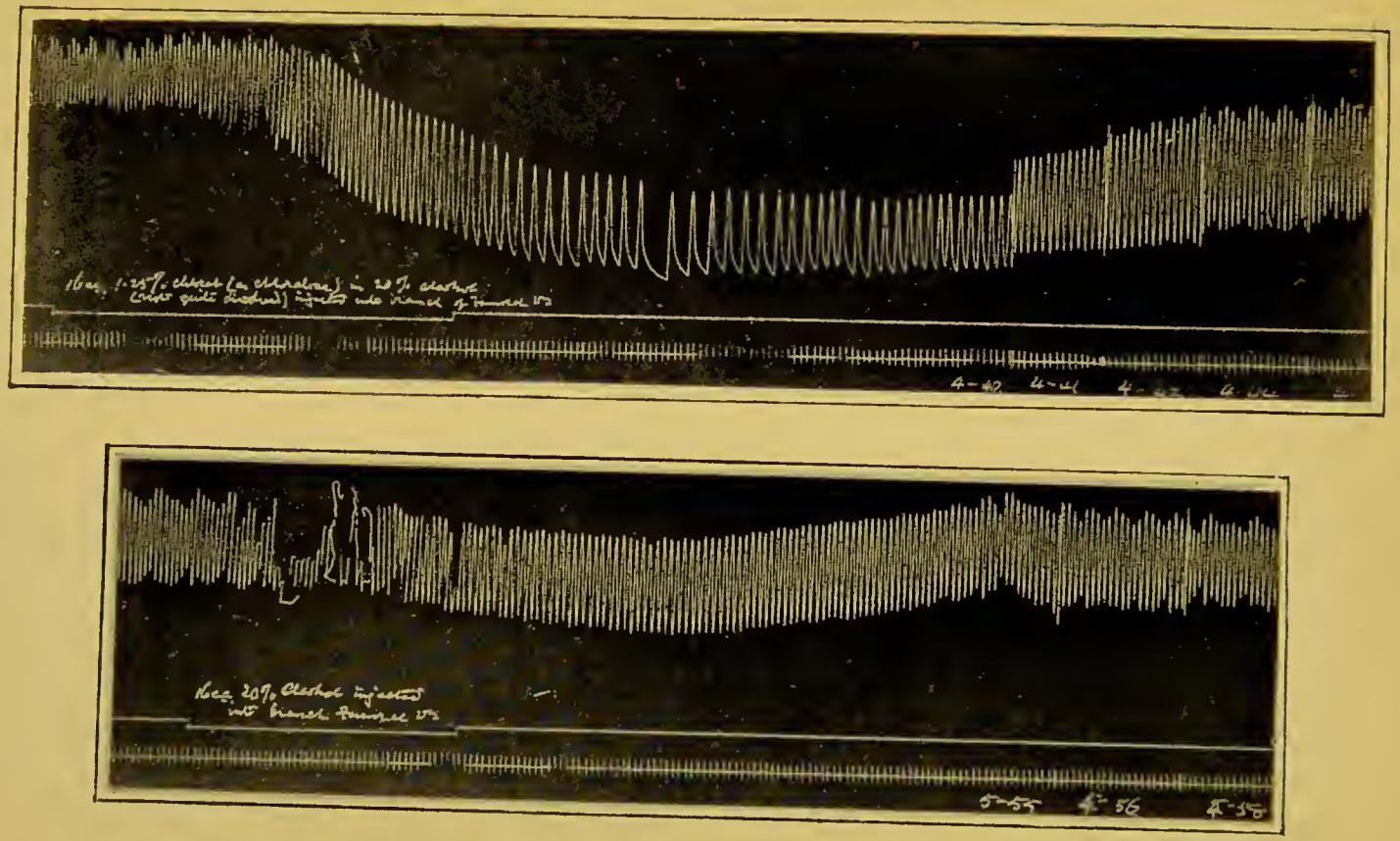
FIG. 10 B



Chloralamide. *Rabbit weighing 1730 grammes. (P. 264. R. 43.) 11.15 : 5 c.c. $\frac{1}{30}$ chloral (as formamide) injected into marginal vein of ear. 11.20 : 2½ c.c. ditto. 11.25 : 2½ c.c. ditto. 11.25 : Operation commenced. × 1.22 to 1 25 : 5 c.c. chloral as hydrate injected into jugular vein. + 2.34 to 2.36 : 5 c.c. ditto.*

FIG. 11.

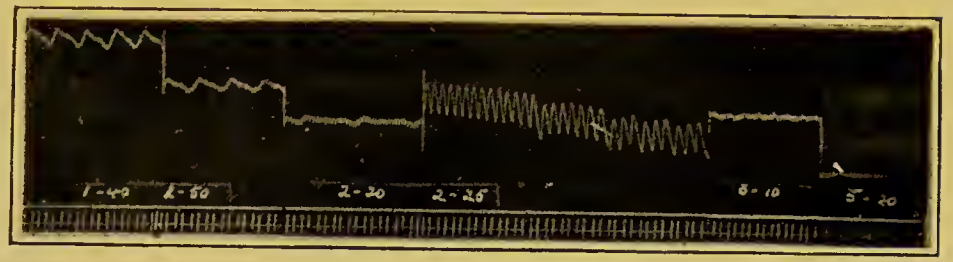
EFFECT OF CHLORALOSE ON BLOOD-PRESSURE.



Dog weighing 9040 grammes, as before (vide Fig. 7). Lower tracing = effect of alcohol given without chloralose.

FIG. 12.

EFFECT OF CHLORALOSE ON BLOOD-PRESSURE.



Rabbit weighing 1420 grammes. (P. 150. R. 240. T. 33·7° C.) 11·37 : 0·96 gramme chloralose (= 0·25 gramme per kilogramme chloral) suspended in water injected into stomach. 12·37 : Laid on side : nystagmus. 1·25 : Operation commenced. 2·25 : Artificial respiration.

FIG. 13.

EFFECT OF URETHANE ON BLOOD-PRESSURE WHEN INJECTED INTRAVENOUSLY.

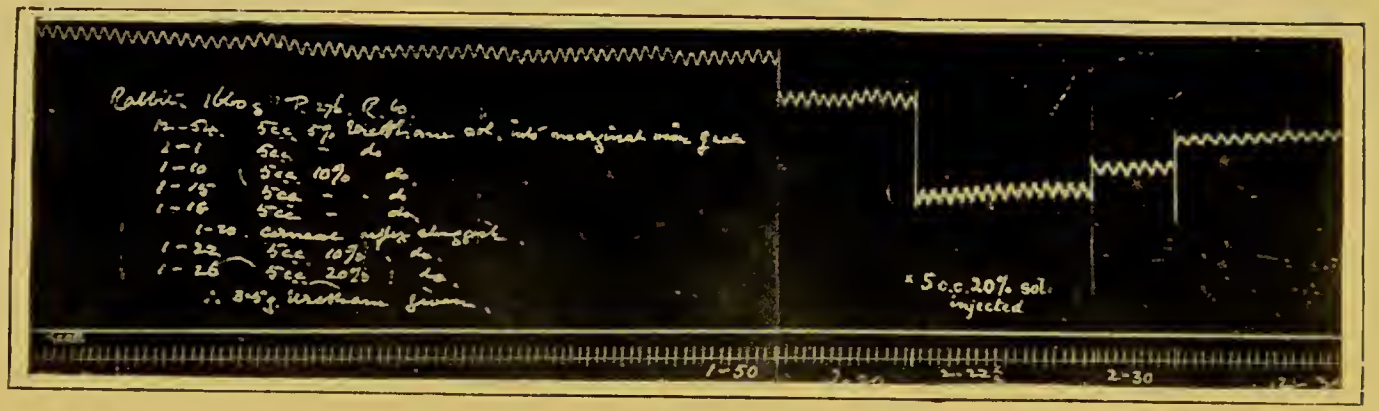


FIG. 14 A.

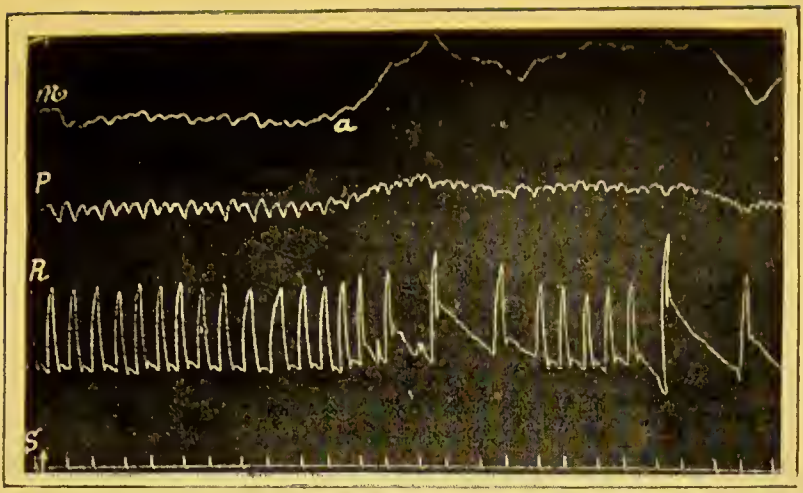


FIG. 14 B.

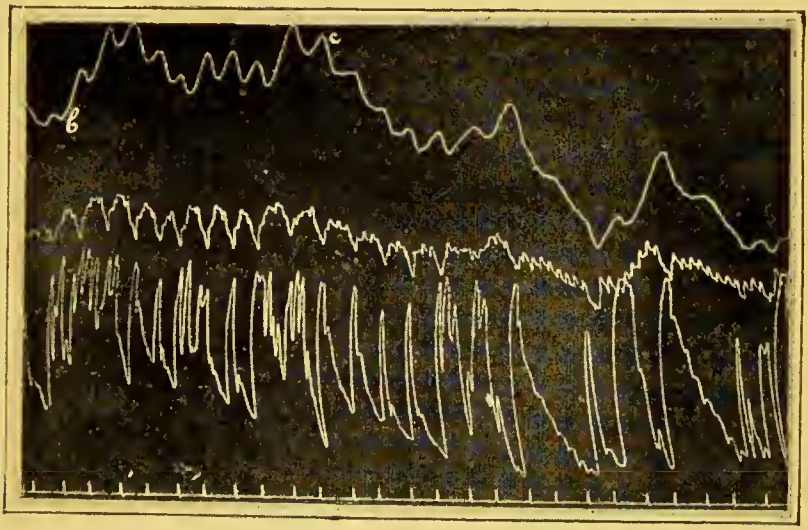
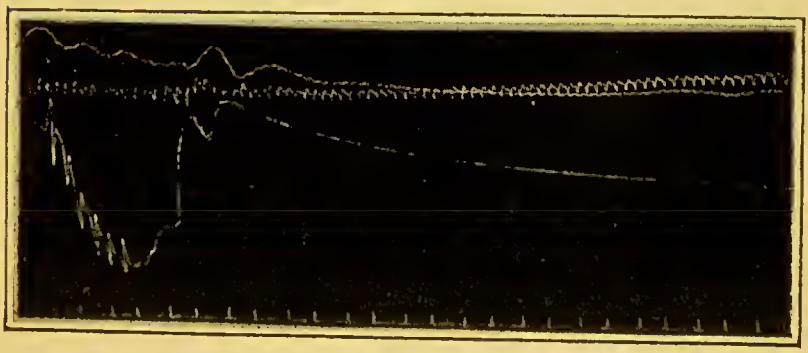
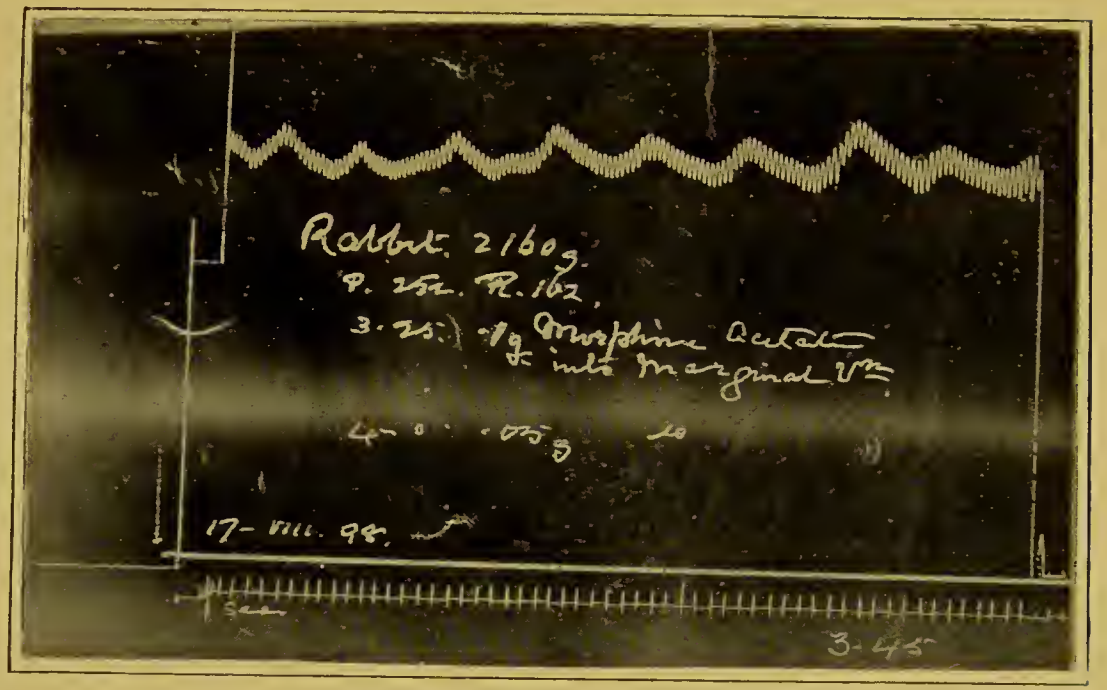


FIG. 14 C.



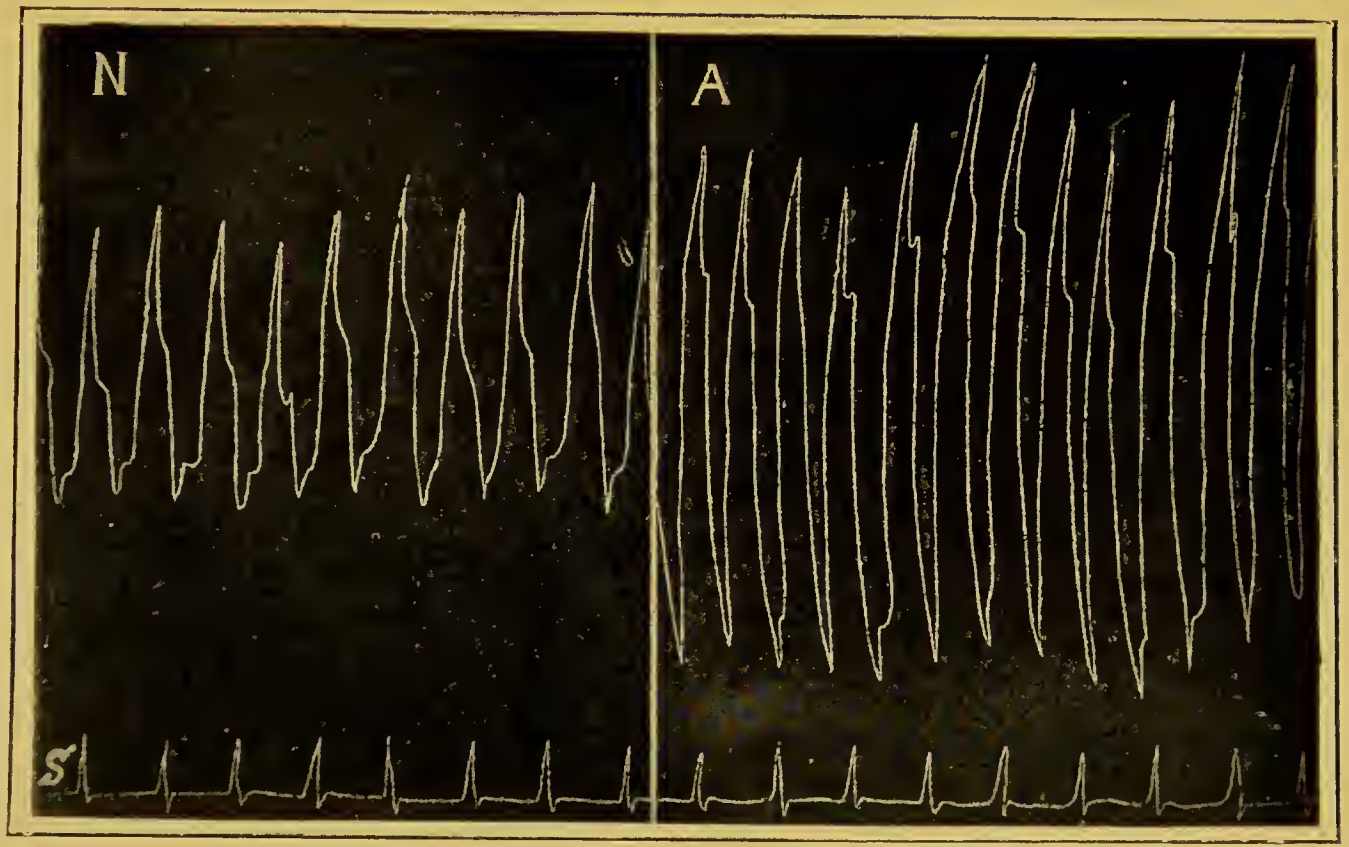
Effects of a venous injection of 8 centigrammes of morphine hydrochioride. The arrow on the line s, Tracing A, indicates the moment of injection. M, Blood-pressure. P, Pulse. R, Respiration. The three tracings, A, B, C, follow one another without interruption, one being the immediate continuation of the other. (Reduction one-third.

FIG. 15.



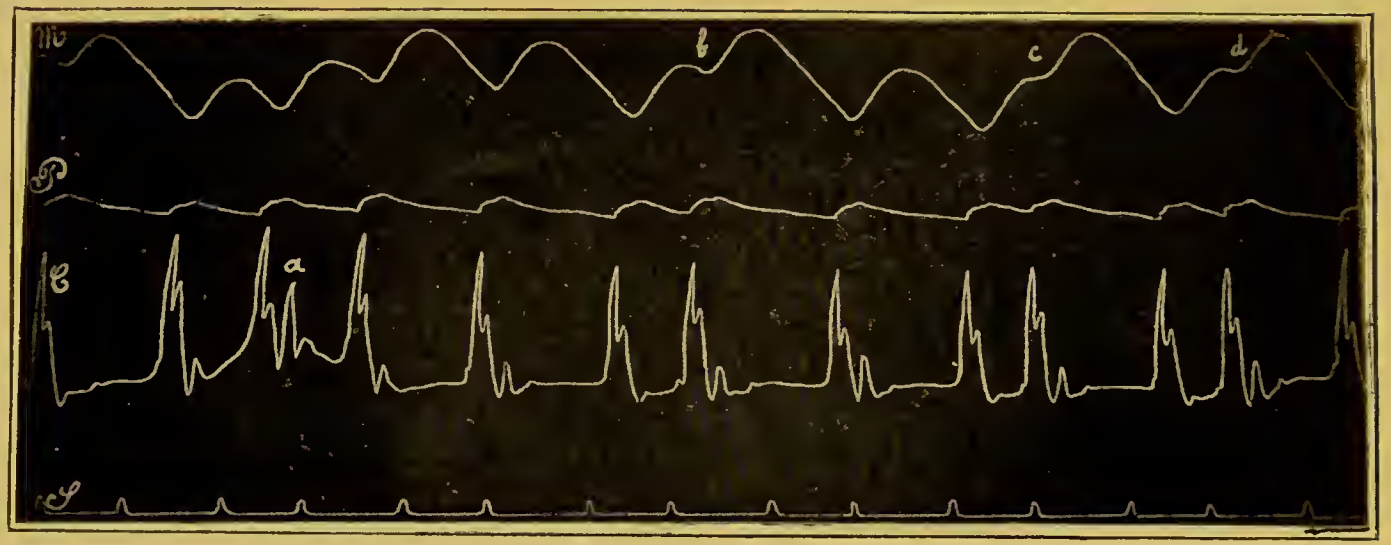
Effect of 0·1 gramme of morphine acetate on blood-pressure when injected intravenously.

FIG 16.



Cardiogram—sheep. N = Normal tracc. A = After 0·25 gramme morphine hydrochloride.

FIG. 17.



Dog two and a half hours after morphine. M, Blood-pressure. P, Pulse. C, Cardiogram. a = Abortive beat.